

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**203469Orig1s000**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

## EXCLUSIVITY SUMMARY

NDA # 203469

SUPPL #

HFD #

Trade Name Iclusig®

Generic Name Ponatinib Hydrochloride

Applicant Name ARIAD Pharmaceuticals

Approval Date, If Known

### PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES  NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES  NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

N/A

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES  NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES  NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

N/A

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES  NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

## **PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES**

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES  NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)  
IF "YES," GO TO PART III.

**PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS**

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a)

is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES  NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES  NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES  NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES  NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES  NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES  NO

Investigation #2 YES  NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES  NO

Investigation #2 YES  NO



Investigation #1  
!  
!  
YES  ! NO   
Explain: ! Explain:

Investigation #2  
!  
!  
YES  ! NO   
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES  NO

If yes, explain:

=====

Name of person completing form: Lara Akinsanya  
Title: Regulatory Health Project Manager  
Date: October 24, 2012

Name of Office/Division Director signing form:  
Title:

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05; removed hidden data 8/22/12

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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MONSURAT O AKINSANYA  
12/14/2012

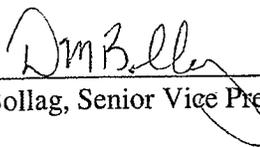
ANN T FARRELL  
12/14/2012

**1.3.3. DEBARMENT CERTIFICATION**

Certification Pursuant to 21 U.S.C Section 335a (k)(1).

On behalf of ARIAD Pharmaceuticals, Inc., I hereby certify that ARIAD did not and will not use in any capacity the services of any individual, partnership, corporation, or association listed on the Debarment List under subsections 306(a) and (b) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C Section 335 (a)(b)) in connection with the New Drug Application (NDA) for 203469.

ARIAD Pharmaceuticals, Inc.

  
\_\_\_\_\_  
Daniel Bollag, Senior Vice President, Regulatory Affairs and Quality

2 July 2012  
Date

# ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION <sup>1</sup>		
NDA # 203469 BLA #	NDA Supplement # BLA Supplement #	If NDA, Efficacy Supplement Type:
Proprietary Name: Iclusig® Established/Proper Name: Ponatinib Hydrochloride Dosage Form: Tablet		Applicant: ARIAD Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A
RPM: Lara Akinsanya		Division: Hematology
<p><b><u>NDA and NDA Efficacy Supplements:</u></b></p> <p>NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)            Efficacy Supplement:   <input type="checkbox"/> 505(b)(1)   <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b><u>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</u></b></p> <p>Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> This application does not rely upon a listed drug.  <input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> This application relies on (explain)</p> <p><b><u>For ALL (b)(2) applications, two months prior to EVERY action, review the information in the 505(b)(2) Assessment and submit the draft<sup>2</sup> to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes   <input type="checkbox"/> Updated   Date of check:</p> <p><b>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</b></p>
❖ Actions		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>March 27, 2013</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input checked="" type="checkbox"/> None

<sup>1</sup> The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 5) lists the documents to be included in the Action Package.

<sup>2</sup> For resubmissions, (b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).

<p>❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received?                  Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<p><input checked="" type="checkbox"/> Received</p>
<p>❖ Application Characteristics <sup>3</sup></p>	
<p>Review priority: <input type="checkbox"/> Standard <input checked="" type="checkbox"/> Priority                  Chemical classification (new NDAs only): 1</p> <p> <input checked="" type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input checked="" type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input checked="" type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC             </p> <p>                 NDAs: Subpart H <input checked="" type="checkbox"/> Accelerated approval (21 CFR 314.510)  <input type="checkbox"/> Restricted distribution (21 CFR 314.520)                  Subpart I <input type="checkbox"/> Approval based on animal studies             </p> <p> <input type="checkbox"/> Submitted in response to a PMR  <input type="checkbox"/> Submitted in response to a PMC  <input type="checkbox"/> Submitted in response to a Pediatric Written Request             </p> <p>                 BLAs: Subpart E <input type="checkbox"/> Accelerated approval (21 CFR 601.41)  <input type="checkbox"/> Restricted distribution (21 CFR 601.42)                  Subpart H <input type="checkbox"/> Approval based on animal studies             </p> <p>                 REMS: <input type="checkbox"/> MedGuide  <input type="checkbox"/> Communication Plan  <input type="checkbox"/> ETASU  <input type="checkbox"/> MedGuide w/o REMS  <input type="checkbox"/> REMS not required             </p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input type="checkbox"/> Yes, dates</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<ul style="list-style-type: none"> <li>Office of Executive Programs (OEP) liaison has been notified of action</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Press Office notified of action (by OEP)</li> </ul>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<ul style="list-style-type: none"> <li>Indicate what types (if any) of information dissemination are anticipated</li> </ul>	<p> <input type="checkbox"/> None  <input checked="" type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input checked="" type="checkbox"/> Other - ASCO Burst             </p>

<sup>3</sup> Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> <li>Is approval of this application blocked by any type of exclusivity?</li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> <li>NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>(b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #        and date exclusivity expires:
<ul style="list-style-type: none"> <li>NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i></li> </ul>	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA #        and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> <li>Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.</li> </ul>	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> <li>Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.</li> </ul>	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified  21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> <li>[505(b)(2) applications] If the application includes a <b>paragraph III</b> certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).</li> </ul>	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> <li>[505(b)(2) applications] For <b>each paragraph IV</b> certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i></li> </ul>	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes  No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "**No**," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes  No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes  No

If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "**No**," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<input type="checkbox"/> Yes <input type="checkbox"/> No
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>4</sup>	December 14, 2012
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action date – December 14, 2012
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	July 30, 2012
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>4</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	July 30, 2012
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	July 30, 2012
<ul style="list-style-type: none"> <li>❖ Proprietary Name             <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> <li>• Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name.</li> </ul> </li> </ul>	Acceptability Letter – 8/21/12 Review Acceptability – 8/20/12
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input checked="" type="checkbox"/> RPM 10/5/12 <input checked="" type="checkbox"/> DMEPA 11/27/12 <input checked="" type="checkbox"/> DMPP/PLT (DRISK) PLT – 12/3/12 <input checked="" type="checkbox"/> ODPD (DDMAC) 11/29/12 <input type="checkbox"/> SEALD <input type="checkbox"/> CSS <input type="checkbox"/> Other reviews
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>5</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	RPM Filing Review- 10/5/12
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents  <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a> </li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP             <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action
<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC _____ If PeRC review not necessary, explain: <u>Orphan Drug</u></li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Included

<sup>5</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent ( <i>include certification</i> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications ( <i>letters, including response to FDRR (do not include previous action letters in this tab), emails, faxes, telecons</i> )	December 5; November 30, 29, 19, 16, 15(2), 6(2), 5, 2; October 29, 25, 22, 18(2), 12(3), 5(2), 2, 1, 1; September 28, 24, 20(2), 17, 13(3), 11, 7(2), 4; August 24, 22, 20, 10
❖ Internal memoranda, telecons, etc.	ONDQA TCON minutes – 11/2/12 DHP TCON minutes- 11/1/12
❖ Minutes of Meetings	
• Regulatory Briefing ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting ( <i>indicate date of mtg</i> )	<input checked="" type="checkbox"/> N/A or no mtg
• Pre-NDA/BLA meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg pre-NDA/CMC- 06/07/12 pre-NDA - 02/16/12
• EOP2 meeting ( <i>indicate date of mtg</i> )	<input type="checkbox"/> No mtg 02/10/11
• Other milestone meetings (e.g., EOP2a, CMC pilots) ( <i>indicate dates of mtgs</i> )	
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available ( <i>do not include transcript</i> )	
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/14/12
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/13/12
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None addendum – 12/5/12; 12/3/12
PMR/PMC Development Templates ( <i>indicate total number</i> )	<input type="checkbox"/> None 10 (9PMRs/1PMC)
<b>Clinical Information<sup>6</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	11/19/12, Cosigned clinical review signed on 11/19/12
• Clinical review(s) ( <i>indicate date for each review</i> )	11/19/12 09/28/12- filing review
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not ( <i>indicate date of review/memo</i> )	see Page 18 of Clinical Review dated 11/19/12
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None CDRH – 10/5/12
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input checked="" type="checkbox"/> Not applicable

<sup>6</sup> Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>)</li> <li>REMS Memo(s) and letter(s) (<i>indicate date(s)</i>)</li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>)</li> </ul>	<input type="checkbox"/> None 11/28/12
❖ DSI Clinical Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested Review Summary – 9/26/12
<b>Clinical Microbiology</b> <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
Clinical Microbiology Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 11/17/12, Cosigned Stats review signed on 11/16/12
Statistical Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 11/16/12, Cosigned Stats review- signed on 11/16/12
Statistical Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 11/16/12, 11/14/12- filing review
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/5/12, Cosigned ClinPharm review signed on 12/4/12
Clinical Pharmacology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/5/12, Cosigned ClinPharm review signed on 12/4/12
Clinical Pharmacology review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 12/4/12 11/30/12 – QT-IRT Review 10/2/12- filing review
❖ DSI Clinical Pharmacology Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None
<b>Nonclinical</b> <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 11/19/12
• Supervisory Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 11/19/12
• Pharm/tox review(s), including referenced IND reviews ( <i>indicate date for each review</i> )	<input type="checkbox"/> None 11/19/12 9/28/12- filing review
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies ( <i>indicate date for each review</i> )	<input checked="" type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input checked="" type="checkbox"/> None
❖ DSI Nonclinical Inspection Review Summary ( <i>include copies of DSI letters</i> )	<input checked="" type="checkbox"/> None requested

<b>Product Quality</b> <input type="checkbox"/> None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>	<input checked="" type="checkbox"/> None
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 11/20/12, Cosigned Final Review signed on 11/20/12, Initial Review - 10/4/12
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>	<input type="checkbox"/> None Final Review-11/20/12, Initial Review - 10/3/12 9/28/12- filing review
❖ Microbiology Reviews <input checked="" type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (OMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>	<input type="checkbox"/> Not needed 10/24/12 9/5/12- filing review
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>	<input type="checkbox"/> None Biopharmaceutics Review – 11/19/12 10/3/12- filing review
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>	Page 123 of Product Quality Final Review dated, 11/20/12
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
❖ Facilities Review/Inspection	
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites<sup>7</sup>)</i>	Date completed: <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>	<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

<sup>7</sup> I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

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MONSURAT O AKINSANYA  
12/14/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Wednesday, December 05, 2012 4:52 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** NDA 203469 (ponatinib) - FDA Proposed MedGuide - - DUE December 10, 2012

**Attachments:** FDA proposed MG\_NDA 203469\_120512\_secure.doc

Dear Andrew Slugg,

Please see attached revised draft of the Medication Guide for NDA 203469.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)



FDA proposed  
G\_NDA 203469\_120

After you have made the changes, please send me the revised tracked change before you make your official submission electronically.

Please provide a revised PI to me by **Monday, December 10, 2012**.

Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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MONSURAT O AKINSANYA  
12/05/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Friday, November 30, 2012 11:41 AM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** NDA 203469 (ponatinibl) - FDA Proposed PI - - DUE December 3, 2012

**Attachments:** FDA proposed PI\_NDA 203469\_113012\_secure.doc; N203469 General comments to Sponsor.doc

Dear Andrew Slugg,

Please see attached revised draft of the PI for NDA 203469.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with
- Edit over the ones that you do not agree with (do not reject any changes that the FDA proposed)



FDA proposed  
[NDA 203469\_113.

Also attached are general comments to the PI that we would like you to consider.



N203469 General  
comments to Sp...

After you have made the changes, please send me the revised tracked change before you make your official submission electronically.

Please provide a revised PI to me by **Monday, December 3, 2012**.

Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
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MONSURAT O AKINSANYA  
11/30/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Thursday, November 29, 2012 5:05 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Nov 29 DMEPA Information Request: NDA 203469/ponatinib DUE 12/5

Dear Andrew Slugg,

Please respond to the following information request from the Division of Medication Error Prevention and Analysis (DMEPA) regarding: [Container Labels 15 mg and 45 mg](#)

1. Ensure the established name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Additionally, the established name should have a prominence commensurate with the prominence of the proprietary name in accordance with 21 CFR 201.10(g)(2).
2. Delete the line that appears between the proprietary name and the established name as it is intervening matter in accordance with 21 CFR 201.10(a).
3. Remove the route of administration “for oral use” from the finished dosage form statement. The route of administration should appear on the label if the intended route of administration is other than oral.
4. Delete the yellow graphic that appears above the letter ‘i’ in the proprietary name as this graphic distracts the end user’s attention from the proprietary name, making it difficult to read.
5. Revise the proprietary name on the container label to title case (i.e. Iclusig) to improve the readability of the proprietary name.
6. Revise the container label to follow the recommended format: proprietary name followed by established name and dosage form immediately underneath the proprietary name. For example,  

Iclusig  
(Ponatinib) Tablets
7. Delete or minimize the red circle graphic in the Applicant’s logo appearing below the statement of strength on the container label. This graphic distracts from the most important information on the principle display panel such as the proprietary name, established name, and statement of strength.
8. The proprietary name and the 45 mg strength share the same blue color font. However, the use of the same color font for the proprietary name and product’s strength minimizes the difference between the strengths, which may lead to wrong strength selection errors. Thus, revise the color font of the proprietary name or the 45 mg strength, so that the strength and the proprietary name appear in its own unique color and the color does not overlap with any other colors utilized in highlighting the strengths.
9. Remove the (b) (4) the Dosage and Use information. This is standard information that appears on all labels; thus, does not require special highlighting.
10. Move NDC number to be further away from the net quantity. Currently, NDC number and the net quantity appear together, which reduces the readability of the NDC number.
11. Unbold the statement of net quantity. Currently the net quantity is in bold font and has more

prominence than other important information such as established name and NDC number.

Please respond to the above Information Request by **Wednesday, December 5, 2012**.

Thank you  
Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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MONSURAT O AKINSANYA  
11/29/2012

**From:** Martin, Jewell  
**To:** ["Andrew P. Slugg"](#)  
**Subject:** NDA 203469 Information Request  
**Date:** Monday, November 19, 2012 9:57:00 AM

---

Andrew,

Please provide written confirmation today, Monday, November 19, 2012, indicating that ARIAD agrees to modify the Identification, Content uniformity, Assay, and Impurities method to address the concern of the FDA methods validation laboratory and submit an updated method and its validation within 3 months, post approval via a CBE-30 supplement.

Best,

Jewell

**Jewell D. Martin, MA, MBA, PMP**  
Product Quality Regulatory Project Manager  
Office of New Drug Quality Assessment  
Food and Drug Administration  
White Oak Building 21, Rm 2625  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
(301) 796-2072  
[jewell.martin@fda.hhs.gov](mailto:jewell.martin@fda.hhs.gov)

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/s/  
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JEWELL D MARTIN  
11/19/2012

**Akinsanya, Lara**

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**From:** Akinsanya, Lara  
**Sent:** Friday, November 16, 2012 7:59 AM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Nov 16 Clinical Information Request: NDA 203469/ponatinib DUE 11/19  
**Attachments:** IR 11-15-12.doc

Dear Andrew Slugg,

Please respond to the attached Clinical Information Request by **Monday, November 19, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

1. Prepare a revised label that updates the safety and exposure data using the updated data cut-off used in the 120-day safety update (23 July 2012).

2. The Division adjudicated the following findings in the efficacy analyses. Provide a justification for each case that you disagree with the FDA adjudicated results.

Adjudication for Major Hematologic Response

SUBJID	Cohort	Applicant's analysis	FDA analysis	Justification
938-012	AP R/I	MaHR (NEL)	Non-responder	MaHR at baseline
948-007	AP T315I	MaHR (CHR)	Non-responder	No labs or bone marrow prior to first dose.
955-002	AP R/I	MaHR (NEL)	Non-responder	No labs or bone marrow prior to first dose.
956-001	AP R/I	MaHR (CHR)	Non-responder	MaHR at baseline
957-010	AP T315I	MaHR (CHR)	Non-responder	MaHR at baseline

Adjudication for Duration of Major Hematologic Response (Note: PDDT field used to define event)

SUBJID	Cohort	Applicant's analysis	FDA adjudication	Justification*
008-002	Ph+ ALL R/I	Censored on D127	Event on D96	Investigator-assessed PD on D96, received cytarabine and mitoxantrone starting on D101, death due to PD on D <sup>(b) (6)</sup>
017-010	Ph+ ALL T315I	Censored on D176	Event on D117	Investigator-assessed PD on D117
048-007	BP-CML T315I	Censored on D100	Event on D67	Investigator-assessed PD on D67, received cytarabine and mitoxantrone starting on D69, death due to PD on D <sup>(b) (6)</sup>
078-001	BP-CML T315I	Censored on D114	Event on D84	Investigator-assessed PD on D84, received cytarabine and daunorubicin starting on D99
128-003	AP-CML R/I	Censored on D195	Event on D164	Investigator-assessed PD on D164, received busulfan, flurabine, and ATG conditiong starting on D169

\*In all cases, the last dose of ponatinib was on the date of investigator-assessed PD.

Note: Reference date is first dose date of ponatinib.

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MONSURAT O AKINSANYA  
11/16/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Thursday, November 15, 2012 7:06 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** FDA Proposed PMRs and PMC for ponatinib - NDA 203469

**Attachments:** FDA Proposed PMRs\_PMCs\_Ponatinib\_111512.doc

Dear Andrew Slugg,

As we continue our review of your NDA, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials (see attached list) are necessary as post-marketing requirements (PMRs), and post-marketing commitments (PMCs), based on the data available to date. These brief summaries are intended to describe the main trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by teleconference if needed.



FDA Proposed  
MRs\_PMCs\_Ponatin.

Upon mutual agreement, we will ask you to submit an official copy of the PMR trials to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Milestones only need month and year. For milestone calculations purposes only, assume that an approval occurs on the PDUFA date.

Final PMR designation numbers will be assigned later. Please respond by **Monday, November 19, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)



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PMR (5) Description: Conduct a dedicated drug interaction trial in humans to determine the effect of coadministration of the strong CYP3A4 inducer rifampin on the pharmacokinetics of ponatinib in healthy subjects.

---

PMR Schedule Milestones: Preliminary Protocol Submission 06/2012  
Final Protocol Submission: 06/2012  
Study/Trial Completion: 06/2013  
Final Report Submission: 12/2013  
Other: \_\_\_\_\_ MM/YYYY

---

PMR (6) Description: Conduct a dedicated hepatic impairment trial in humans to determine the effect of hepatic impairment (i.e., Child-Pugh classes A, B, and C) on the pharmacokinetics of ponatinib when compared to healthy subjects.

---

PMR Schedule Milestones: Preliminary Protocol Submission 06/2012  
Final Protocol Submission: 06/2012  
Study/Trial Completion: 06/2013  
Final Report Submission: 12/2013  
Other: \_\_\_\_\_ MM/YYYY

---

PMR (7) Description: To characterize exposure:response for ponatinib:  
Collect sparse PK from all patients in a clinical trial. Your ongoing trial AP24534-12-301 may be suitable for this objective. Exposure-response analysis should be conducted for both efficacy and safety endpoints. Based on the results of these analyses, a trial to evaluate lower dose or an alternate dosing regimen of ponatinib may be necessary.

---

PMR Schedule Milestones: Preliminary Protocol Submission 01/2013  
Final Protocol Submission: 03/2013  
Study/Trial Completion: 1/2015  
Final Report Submission: 6/2015  
Other: \_\_\_\_\_ MM/YYYY

---

PMR (8) Description: Conduct a dedicated clinical trial in humans to determine the effect of multiple doses of lansoprazole on the pharmacokinetics of ponatinib in healthy subjects.

---

PMR Schedule Milestones: Preliminary Protocol Submission 06/2012  
Final Protocol Submission: 06/2012  
Study/Trial Completion: 06/2013  
Final Report Submission: 12/2013  
Other: \_\_\_\_\_ MM/YYYY

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## FDA proposed Post Marketing Commitments for NDA 203469/ Iclusig® (Ponatinib tablets)

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PMC (1) Description: Evaluate the in vitro potential for the displacement of ponatinib, at a therapeutic concentration, from its protein binding sites in human plasma following addition of frequently used highly protein-bound co-medications. Positive findings from this in vitro study may require additional trials in vivo.

---

PMC Schedule Milestones:	Preliminary Protocol Submission	<u>01/2013</u>
	Final Protocol Submission:	<u>03/2013</u>
	Study/Trial Completion:	<u>01/2014</u>
	Final Report Submission:	<u>03/2014</u>
	Other: _____	<u>MM/YYYY</u>

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MONSURAT O AKINSANYA  
11/15/2012

**From:** Martin, Jewell  
**To:** ["Andrew P. Slugg"](#)  
**Subject:** NDA 203469 Information Request  
**Date:** Thursday, November 15, 2012 11:08:00 AM

---

Andrew,

Please provide a written response for the information requested by Monday, November 19, 2012.

Provide an updated drug substance specification table to reflect revisions to acceptance criteria for assay, specified impurity (b) (4) and particle size distribution (as provided in your response dated October 12, 2012).

In addition to formally submitting your response, please send me a courtesy copy via email. If you have any questions please do not hesitate to contact me.

Please confirm receipt of this email.

Best,

Jewell

**Jewell D. Martin, MA, MBA, PMP**  
Product Quality Regulatory Project Manager  
Office of New Drug Quality Assessment  
Food and Drug Administration  
White Oak Building 21, Rm 2625  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
(301) 796-2072  
[jewell.martin@fda.hhs.gov](mailto:jewell.martin@fda.hhs.gov)

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JEWELL D MARTIN  
11/15/2012

**From:** Martin, Jewell  
**To:** ["Andrew P. Slugg"](#)  
**Subject:** NDA 203469 Information Request  
**Date:** Tuesday, November 13, 2012 3:58:00 PM

---

Andrew,

Please provide a written response for the information requested by Thursday, November 15, 2012.

We refer to your Method for Ponatinib (AP24534) for Identification, Content Uniformity, Assay and Impurities. Based on evaluation by the Division of Pharmaceutical Analysis of FDA, we have the following comment pertaining to this method:

Two similar impurity marker solutions are prepared for the two methods. In "HPLC Analysis of (b) (4)

[REDACTED]

Therefore, we recommend employing the impurity marker preparation procedure used in the method "HPLC Analysis of (b) (4)" for both methods to avoid making dilutions with a suspension. Submit the revised method.

In addition to formally submitting your response, please send me a courtesy copy via email. If you have any questions please do not hesitate to contact me.

Please confirm receipt of this email.

Best,  
Jewell

**Jewell D. Martin, MA, MBA, PMP**  
Product Quality Regulatory Project Manager  
Office of New Drug Quality Assessment  
Food and Drug Administration  
White Oak Building 21, Rm 2625

10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002

(301) 796-2072

[jewell.martin@fda.hhs.gov](mailto:jewell.martin@fda.hhs.gov)

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JEWELL D MARTIN  
11/15/2012

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 7, 2012

TO: NDA 203469 File

THROUGH: Lara Akinsanya

FROM: Team

SUBJECT: November 1, 2012 face to face meeting with ARIAD Pharmaceuticals

APPLICATION/DRUG: NDA 203469/ponatinib

<b>Details of Meeting Discussion</b>	<p>The Division had a face-to-face meeting with ARIAD to discuss the benefit-risk of ponatinib for ARIAD's proposed indication. Specifically, the Division discussed its concerns regarding the risks including liver failure, arterial occlusive and thromboembolic events observed in the safety population.</p> <p>The Division discussed its position outlined in the attached FDA meeting package shared with the sponsor prior to the meeting. The Sponsor also discussed its position described in a formal written response to the Division (also attached).</p> <p>In conclusion, The Division asked the Sponsor to Submit a revised proposed labeling (PI and PPI) that includes the safety issues identified by the Division as described in the attached FDA meeting package. The Sponsor agreed to provide a revised label to the FDA.</p>
<b>RPM</b>	Lara Akinsanya, M.S.

**FDA Attendees**

<b>NAME</b>	<b>TITLE</b>
Richard Pazdur, M.D.	Office Director
Anthony Murgio, M.D.	Associate Office Director
Ann Farrell, M.D.	Division Director
Edvardas Kaminskas, M.D.	Deputy Division Director
Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC	Clinical Team Leader
Angelo De Claro, M.D.	Medical Officer
Haleh Saber, Ph.D.	Supervisory, Pharmacologist
Stacey Ricci, Ph.D.	Pharmacology/Toxicology Reviewer
Perdro DelValle, Ph.D.	Pharmacology/Toxicology Reviewer
Qin Ryan, M.D., Ph.D.	Medical Officer for Safety
Diane Leaman, B.S.	Safety Regulatory Project Manager
Li Zhang, Pharm.D.	Clinical Pharmacology Reviewer
Nitin Mehrotra, Pharm.D.	Clinical Pharmacology Reviewer
Hongshan Li, Pharm.D.	Clinical Pharmacology Reviewer
Rachelle Lubin, Pharm.D.	Clinical Pharmacology Reviewer
Joseph Grillo, Pharm.D.	Clinical Pharmacology Reviewer
Julie Bullock, Pharm.D.	Team Leader, Clinical Pharmacology
Ebla Ali Ibrahim, M.S.	Acting Lead Regulatory Project Manager
Lara Akinsanya, M.S.	Regulatory Project Manager
Mark Rothmann, Ph.D.	Statistical Team Leader
Kyung Lee, Ph.D.	Statistician

**Sponsor Attendees**

<b>NAME</b>	<b>TITLE</b>
Daniel Bollag, Ph.D.	Senior Vice President, Regulatory Affairs and Quality
Maureen Curran, RN BSN	Senior Director, Pharmacovigilance and Risk Management
Timothy Clackson, Ph.D.	President, Research and Development, and Chief Scientific Officer
Frank Haluska, M.D., Ph.D.	Senior Vice President, Clinical Research & Development, and Chief Medical Officer
Shirish Hirani, Ph.D.	Vice President, Program and Alliance Management
Ron Knickerbocker, Ph.D.	Vice President, Biomedical Data Sciences and Information
Julia G Laguette, M.D.	Senior Medical Director, Pharmacovigilance and Risk Management
Andrew Slugg, M.S., M.B.A.	Director, Regulatory Affairs
Christopher Turner, M.D.	Senior Medical Director, Clinical Affairs
Kumiko Yanase, M.D.	Senior Medical Director, Pharmacovigilance and Risk Management

(b) (4)

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MONSURAT O AKINSANYA  
11/16/2012

**Akinsanya, Lara**

---

**From:** Akinsanya, Lara  
**Sent:** Tuesday, November 06, 2012 1:58 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** FDA Response/Information Request - NDA 203469 - ARIAD Proposed NOV 5 Labeling

Dear Andrew Slugg,

The Division rejects your proposed label. Submit a revised label on or before 9 AM EST on Monday, November 12, 2012 that includes the following changes:

1. Box warning for arterial thromboembolic events, arterial stenosis, and hepatic toxicity. We do not accept your justification. The Division's position regarding the inclusion of box warnings is firm. We refer you to our discussion during our face-to-face meeting on November 1, 2012.

2.  (b) (4)

3. Revise the language in the following sections: Highlights, Warnings and Precautions, and Dosage and Administration, to provide detailed information as outlined in Section C of "Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format" at [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf)

Thanks  
Lara

---

**From:** Andrew P. Slugg [mailto:Andrew.Slugg@ariad.com]  
**Sent:** Monday, November 05, 2012 7:34 PM  
**To:** Akinsanya, Lara  
**Subject:** RE: Meeting Information Package - NDA 203469 - Nov 1 Meeting with FDA  
**Importance:** High

Dear Lara,

Thanks again for your call today. In follow-up to the 25 October 2012 request below and our meeting last week, attached please find the revised draft label (clean version in MS Word with redline PDF), patient prescribing information (clean version in MS Word with redline PDF) and a companion response document that provides additional detail on ARIAD's approach to the revisions. These documents and the rest of the submission will be included an official amendment to the NDA and submitted tomorrow.

If you have any questions, please don't hesitate to contact me.

All the best,

Andrew

**Andrew P Slugg**

Director, Regulatory Affairs  
ARIAD Pharmaceuticals, Inc  
26 Landsdowne Street  
Cambridge, MA 02139-4234  
*Mobile: +1 617 710 1840*  
*Office: +1 617 503 7097*

---

**From:** Akinsanya, Lara [mailto:Lara.Akinsanya@fda.hhs.gov]  
**Sent:** Thursday, October 25, 2012 4:23 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Meeting Information Package - NDA 203469 - Nov 1 Meeting with FDA

Dear Andrew Slugg,

Please find attached, FDA meeting information documents to help you prepare for the meeting with us next week. This material is shared to promote a collaborative and successful discussion at the meeting.

Please send me, **by Noon on Wednesday, October 31, 2012**, a written response to each question contained in the meeting package. A revised Package Insert and Patient Package Insert will also need to be submitted to the Agency, by **COB on Friday, November 2, 2012**.

Also remember to send me a copy of your slide presentation/handouts, if any, for projection at the meeting unless you plan to bring in your own computer and projector.

Thank You

Lara Akinsanya

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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MONSURAT O AKINSANYA  
11/06/2012

**Akinsanya, Lara**

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**From:** Akinsanya, Lara  
**Sent:** Tuesday, November 06, 2012 9:48 AM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Nov 6 NonClinical Information Request: NDA 203469/ponatinib DUE 11/9

Dear Andrew Slugg,

During the review of Primary Pharmacology study ARP280, a discrepancy was found regarding the IC50 value for KDR/VEGFR2. Table 2 lists the IC50 value as 560 nM, but the raw data provided indicates that it is approximately two orders of magnitude lower than this. The value of 560 nM also is in conflict with the results published in the O'Hare et al. 2010 *Cancer Cell* paper which lists an IC50 of 1.5 nM.

1. Provide an explanation for this discrepancy.
2. Indicate whether the data provided in the NDA is from the same analysis conducted by the Reaction Biology Corporation and published in *Cancer Cell*.
3. Verify whether all results provided in Table 2 of Study ARP280 are accurate.

Please respond to the above Information Request by **Friday, November 9, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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MONSURAT O AKINSANYA  
11/06/2012

**Akinsanya, Lara**

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**From:** Akinsanya, Lara  
**Sent:** Monday, November 05, 2012 12:11 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Nov 5 QT-IRT Information Request: NDA 203469/ponatinib DUE 11/6

Dear Andrew Slugg,

- We are not able to locate the ECGs and adverse event data referenced in your NDA submission. Please submit the referenced ECGs or provide us with a link to their location if they have already been submitted.

Please respond to the above Information Request by **Tuesday, November 6, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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MONSURAT O AKINSANYA  
11/05/2012

## MEMORANDUM OF MEETING MINUTES

**MEETING DATE:** November 2, 2012  
**TIME:** 10:00 AM – 10:15AM(EST)  
**LOCATION:** TCON/CDER WO 2560  
**APPLICATION:** NDA 203469  
**DRUG NAME:** Ponatinib  
**TYPE OF MEETING:** FDA initiated TCON  
**MEETING CHAIR:** Kareen Riviere, Biopharmaceutics Reviewer  
**MEETING RECORDER:** Jewell Martin, Regulatory Health Project Manager  
**MEETING PURPOSE:** The purpose of the TCON to discuss the dissolution acceptance criteria.

### **FDA Attendees:**

Sandra Suarez-Sharp, PhD, Biopharmaceutics Team Lead, ONDQA  
Kareen Riviere, PhD, Biopharmaceutics Reviewer, ONDQA  
Janice Brown, MS, CMC Lead, ONDQA  
Jewell Martin, MA,MBA, PMP, Regulatory Project Manager, ONDQA

### **ARIAD Attendees:**

Tim Clackson, President Research and Development and Chief Scientific Officer  
Daniel Bollag, Sr. Vice President Regulatory Affairs and Quality  
Shirish Hirani, Vice President Program Alliance Management  
Chris Murray, Sr. Director Pharmaceutical Development  
John Chaber, Sr. Director Analytical Development  
Andrew Slugg, Director Regulatory Affairs  
Douglas Shorten, Associate Director Program Management  
Nicole Oliynyk, Director Regulatory Affairs CMC  
Constance Emmett, Associate Director Quality Control  
Kristine Nardelli, Sr. Manager Regulatory Affairs CMC  
Caroline Kinross, Sr. CMC Associate Regulatory Affairs

### **Meeting Notes:**

The Agency requested that the sponsor update dissolution acceptance criterion to  $Q = \frac{(b)}{(4)}\%$  at 30 minutes. The Applicant agreed to update dissolution acceptance criterion and formally submit new specifications to NDA.

The Agency asked the applicant to give insight as to why some batches failed  $f_2$  at the new site. The Applicant indicated that tablets manufactured at the new site performed faster due to moisture and that the reference material used was about 12 months old which accounts for the slight moisture affect over time. The Agency asked if having a faster release profile has an impact on the safety. The Applicant stated that the affect tends to plateau after 3 months and does not impact the safety.

Sponsor asked if Agency could submit questions concerning this issue in writing so that they could confer with the appropriate team members. The Agency agreed.

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JEWELL D MARTIN  
11/09/2012

KAREEN RIVIERE  
11/09/2012

**From:** Martin, Jewell  
**To:** ["Andrew P. Slugg"](#)  
**Subject:** NDA 203469 Information Request  
**Date:** Friday, November 02, 2012 1:15:00 PM

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Andrew,

Please provide a written response for the information requested by Wednesday, November 7, 2012.

The Agency is concerned regarding several deficiencies associated with dissolution behavior. These include an apparent slower dissolution with drug product age and a failed  $f_2$  comparison between fresh and one year aged batches.

- Provide specific and detailed information and data as to why some batches failed  $f_2$  at the (b) (4) site and indicate the strategy to control it. Confirm if the faster release profile has an impact on the safety (or if the slower release profile has an impact on efficacy) and provide appropriate data substantiating this phenomenon.
- Based on substantial trends in dissolution profile a shelf life of 12 months will be acceptable.
- In reference to you request to update the impacted CTD sections in the annual report, the Agency recommends that you update your files in the current cycle.

In addition to formally submitting your response, please send me a courtesy copy via email. If you have any questions please do not hesitate to contact me.

Please confirm receipt of this email.

Best,

Jewell

**Jewell D. Martin, MA, MBA, PMP**  
Product Quality Regulatory Project Manager  
Office of New Drug Quality Assessment  
Food and Drug Administration  
White Oak Building 21, Rm 2625  
10903 New Hampshire Avenue  
Silver Spring, MD 20993-0002  
(301) 796-2072  
[jewell.martin@fda.hhs.gov](mailto:jewell.martin@fda.hhs.gov)

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JEWELL D MARTIN  
11/02/2012

**Akinsanya, Lara**

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**From:** Akinsanya, Lara  
**Sent:** Monday, October 29, 2012 12:10 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Oct 29 Clinical Information Request: NDA 203469/ponatinib DUE 11/2

Dear Andrew Slugg,

- Your submitted analysis dataset baserep.xpt (NDA 203469 SDN 28 received 10/24/12) is incomplete. Please resubmit with all the blank cells filled out.

Please respond to the above Information Request before **Friday, November 2, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
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MONSURAT O AKINSANYA  
10/29/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Thursday, October 25, 2012 4:23 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Meeting Information Package - NDA 203469 - Nov 1 Meeting with FDA

**Attachments:** ARIAD Nov 1.doc; v1 Ponatinib\_draft-labeling\_100212.doc

Dear Andrew Slugg,

Please find attached, FDA meeting information documents to help you prepare for the meeting with us next week. This material is shared to promote a collaborative and successful discussion at the meeting.



ARIAD Nov 1.doc  
(36 KB)



v1  
tinib\_draft-labeling\_

Please send me, by **Noon on Wednesday, October 31, 2012**, a written response to each question contained in the meeting package. A revised Package Insert and Patient Package Insert will also need to be submitted to the Agency, by **COB on Friday, November 2, 2012**.

Also remember to send me a copy of your slide presentation/handouts, if any, for projection at the meeting unless you plan to bring in your own computer and projector.

Thank You

Lara Akinsanya

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

**Purpose of Meeting:** The Division requests a face-to-face meeting with ARIAD to discuss the benefit-risk of ponatinib for ARIAD's proposed indication. Specifically, the Division is concerned regarding the risks including liver failure, arterial occlusive and thromboembolic events observed in the safety population.

**Background:** Safety evaluation is difficult in single-arm clinical trials due to the absence of a comparator arm to assess the clinical significance of treatment-emergent adverse events (TEAEs). As such, the Agency has taken the approach of labeling all clinically significant TEAEs regardless of attribution in prior approvals based on single-arm clinical trial(s). Further characterization of these adverse events may be undertaken with randomized clinical trials, and the safety labeling may be revised based on the results of randomized trial data.

**Questions:**

1. The Division rejects your proposed label for Iclusig<sup>®</sup> due to inadequate description of safety results observed from a single-arm clinical trial. Submit a revised proposed label that includes the safety issues identified by the Division (refer to attached Highlights Section). Examine each section of the label and patient prescribing information and update as needed based on the revised list of safety issues in the Box Warnings and Warnings and Precautions Section.

Refer to "Guidance for Industry: Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products—Content and Format" at [www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075096.pdf)

The broad spectrum of kinase inhibition (including inhibition of VEGFR kinases) observed with ponatinib may be a possible explanation for the safety signals identified with ponatinib that were not observed with the other bcr-abl TKIs. As such, please also refer to USPI for FDA-approved TKIs including sorafenib, sunitinib, axitinib, pazopanib, vandetanib, and regorafenib.

- 1.1. In Study 10-201, 51 patients (11%) experienced arterial occlusive or thromboembolic events (AOTE) of any grade. Thirty-four patients (8%) experienced serious AOTE. Refer to (1) ISCHEMIA.xpt dataset that was sent to you on October 22, 2012 for a listing of the events, and (2) Section 3.1.5.2.7 Ischemic Vascular Events of Safety Update #1.

From review of the SAE narratives, the Division identified a safety signal for arterial stenosis in patients who experienced ischemic events. Sixteen patients who experienced myocardial ischemia required revascularization (PTCA, CABG, or both). Four patients who experienced CNS ischemia were documented to have arterial stenosis: bilateral MCA (1 patient); R ICA, R vertebral and basilar (1 patient); carotid artery supraclinoid (1); vertebral and

subclavian artery (1 patient). Four patients who experienced peripheral arterial ischemia required PTCA or bypass surgery. Safety signals for arterial stenosis was also noted from SAE reports in patients treated in your Expanded Access Program.

- 1.2. Regarding hepatic toxicity, refer to Sections 1.1.2.4 and 3.1.5.2.5 of Safety Update #1 (Summary of Clinical Safety).
- 1.3. Regarding hemorrhage, congestive heart failure, rate and rhythm disorders, fluid retention, refer to Sections 3.1.5.2.3, 3.15.2.6, and 3.1.5.2.8 of your Summary of Clinical Safety (Original and Safety Update #1).
- 1.4. Regarding hypertension, the Division recommends that you use the VS dataset for calculation of event rates for hypertension. Use the SAE narratives for hypertension events for text regarding hypertensive crisis.
- 1.5. Regarding tumor lysis syndrome, gastrointestinal perforation, compromised wound healing, and venous thromboembolism, refer to your AE datasets and SAE narratives.

**Question 1a.: Why did you exclude arterial ischemic events and other cardiovascular safety issues in your Warnings and Precautions?**

**Question 1b.: Does ARIAD have any comments regarding the attached Highlights Section, specifically with regards to the Agency's recommendations regarding Box Warnings and Warnings and Precautions?**

2. Seventy-three percent of patients required a dose interruption or dose reduction, such that patients with CP-CML were on the full dose level (45 mg per day) for 50% of the entire treatment duration. Patients with AP-CML were on the full dose level for 60% of the entire treatment duration.

**Question: What are your plans to evaluate lower dose levels or alternative dose schedules in patients with CP-CML or AP-CML?**

**Comments:**

1. The Division recommends that you should designate arterial thromboembolic events, vascular stenosis, or any requirement for a vascular diagnostic or therapeutic procedure as adverse events of special interest, which would require enhanced data collection and submission of narratives for ongoing or planned clinical trials with ponatinib.
2. Revise the informed consent document for 12-301 and investigator's brochure to emphasize the risk for arterial ischemic events and hepatic toxicity, and include the safety issues described in #1.

3. Regarding the data monitoring plan for Study 12-301, explain how you plan to evaluate and address should you observe an excess cardiovascular safety signal in the ponatinib arm as compared to the imatinib arm. We recommend that you have stopping rules for excess cardiovascular toxicity. We also recommend there be a formal DMC review of the safety data at prespecified enrollment numbers.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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MONSURAT O AKINSANYA  
11/01/2012

**Akinsanya, Lara**

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**From:** Akinsanya, Lara  
**Sent:** Monday, October 22, 2012 11:57 AM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Oct 22 Clinical Pharmacology Information Request: NDA 203469/ponatinib DUE 10/23  
**Attachments:** ischemia.xlsx

Dear Andrew Slugg,

For exposure-response analysis on ischemia events (as described in the attached data file ischemia.xlsx), we need the following information for each subject listed in the file:

1. Ponatinib Dose Intensity from the 1<sup>st</sup> dose to the last dose if the ischemia event started after the last dose (TIME1 > 0). Otherwise,
2. Ponatinib Dose Intensity from the 1<sup>st</sup> dose to the dose when ischemia event started (TIME1 <=0).

Please respond to the above Information Request by **Tuesday, October 22**, 2012.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
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MONSURAT O AKINSANYA  
10/22/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Thursday, October 18, 2012 2:49 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Oct 18 Clinical- Information Request : NDA 203469/ponatinib DUE 10/23

**Attachments:** Ischemia.jmp

Dear Andrew Slugg,

Please respond to the following Clinical Information Request:

1. To facilitate our upcoming discussion on November 1, please refer to the attached dataset: ischemia.jmp. Ischemia.jmp dataset is a subset of the AE.xpt dataset submitted in the 120-day safety update. Each row in Ischemia.jmp dataset represents a treatment-emergent (TEAE=1) ischemic event that was selected by the clinical team.



Ischemia.jmp (50  
KB)

2. Please submit the most current versions of the informed consent documents for Study 10-201 and Study 12-301.
  - 3.1 Please submit the most current version of the Data Monitoring Committee (DMC) charter for Study 12-301, as described in Section 18.4.1 of the protocol.
  - 3.2. Provide a status update on enrollment (number of sites open, number of patients enrolled) for Study 12-301.
- 4.1 Please submit a dataset (one row per USUBJID) that lists the baseline Major Hematologic Response (MAHR) and Complete Hematologic Response (CHR) status for all patients in Study 10-201. If the patient is not evaluable for baseline hematologic response, please categorize as "Not Evaluable" rather than "Not in Hematologic Response".
- 4.2. Explain how you determined baseline hematologic response for patients who may have more than one set of baseline hematologic response data available.

Please respond to the above Information Request by **Noon on Tuesday, October 23**, 2012:

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
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MONSURAT O AKINSANYA  
10/18/2012

**Akinsanya, Lara**

---

**From:** Akinsanya, Lara  
**Sent:** Thursday, October 18, 2012 1:47 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Follow Up Questions: Oct 12 Clinical Pharmacology- Information Request : NDA 203469/ponatinib DUE 10/19

Hi Andrew,

The Clinical Pharmacology Team has a few follow up questions listed below:

About the provided datasets lipase\_g.xpt, :

1. All 376 subjects had numerical data for variable "GRADE" . However, 14 of those 376 subjects had no GRADEDI (dose intensity) provided. Please explain why those 14 subjects had no GRADEDI.
2. Total 257 subjects had numerical data for variable "LGRADE" . However, 14 of those 257 subjects had no LGRADEDI (dose intensity) provided. Please explain why those 14 subjects had no GRADEDI.

If those 14 subjects had no AE reported at the same time, please provide the corresponding dose intensity.

About the provided datasets lipase.xpt:

1. Total 46 subjects had no LAB\_LIPA/LIPA\_DI reported. Please explain why.
2. Total 112 subjects had no PANC/PANC\_DI reported. Please explain why.
3. Total 61 subjects had no AE\_LIPAS/AELIP\_DI reported. Please explain why.

If those 46, 112 or 61 subjects had no AE reported at the same time, please provide the corresponding dose intensity.

Please respond to the above Information Request by **Tomorrow, October 19, 2012**

Thanks

Lara

---

**From:** Andrew P. Slugg [mailto:Andrew.Slugg@ariad.com]  
**Sent:** Tuesday, October 16, 2012 9:25 PM

**To:** Akinsanya, Lara

**Subject:** RE: Oct 12 Clinical Pharmacology- Information Request : NDA 203469/ponatinib DUE 10/16

Hi Lara,

I hope all is well. I wanted to follow-up and let you know we submitted a response to the request below, as well as the CMC/Microbiology Information request, earlier today. I have included review copies of each of these responses; however, I have not included the datasets related to the Clinical Pharmacology Information request in this email.

If you have any questions regarding these responses, please let me know.

Kind Regards,

Andrew

**Andrew P Slugg**

Director, Regulatory Affairs

ARIAD Pharmaceuticals, Inc

26 Landsdowne Street

Cambridge, MA 02139-4234

Mobile: +1 617 710 1840

Office: +1 617 503 7097

---

**From:** Akinsanya, Lara [mailto:Lara.Akinsanya@fda.hhs.gov]

**Sent:** Friday, October 12, 2012 6:55 AM

**To:** Andrew P. Slugg

**Cc:** Akinsanya, Lara

**Subject:** Oct 12 Clinical Pharmacology- Information Request : NDA 203469/ponatinib DUE 10/16

Dear Andrew Slugg,

As we need to perform additional analysis on dose-intensity-response relationship, please provide the following information for Study AP24523-10-201:

Matched dose-intensity for each of the following 3 variables of each subject: LAB\_LIPA, PANC, and AE\_LIPAS for dataset LIPASE.xpt (as attached).

Matched dose-intensity for each of the following 3 variables of each subject: AGRADE, LGRADE, and GRADE for dataset LIPASE\_GR.xpt (as attached).

Systolic and diastolic blood pressures at baseline, HYPRD6, HYPRD12 and HYPRDAT of each subject for recently provided datasets ader.xpt and ader3.xpt

Since the rate of hypertension is different between the ader.xpt and the vital signs dataset, please provide the dose-intensity-hypertension dataset based on vital signs data. The dataset should be in similar format to that of ader.xpt and ader3.xpt. Additionally, also include a column which specifies baseline SBP and DBP for each patient.

Please respond to the above Information Request by **Tuesday, October 16, 2012:**

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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MONSURAT O AKINSANYA  
10/18/2012



NDA 203469

## FILING COMMUNICATION

ARIAD Pharmaceuticals Inc.  
Attention: Andrew P. Slugg  
Director, Regulatory Affairs  
26 Landsdowne Street  
Cambridge, MA 02139

Dear Mr. Slugg:

Please refer to your New Drug Application (NDA) dated July 30, 2012, received September 27, 2012, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Iclusig® (ponatinib) 15 mg and 45 mg tablets for oral use.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is March 27, 2013.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by February 27, 2013.

At this time, we are notifying you that, we have not identified any potential review issues. Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

### **PROMOTIONAL MATERIAL**

We will review this application under the provisions of 21 CFR 314 Subpart H – *Accelerated Approval of New Drugs for Serious or Life-Threatening Illnesses*. Unless we otherwise inform you, as required by 21 CFR 314.550, you must submit during the preapproval review period

copies of all promotional materials, including promotional labeling and advertisements, intended for dissemination or publication within 120 days following marketing approval (i.e., your launch campaign). During the preapproval review period, please submit, in triplicate, a detailed cover letter (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI) and patient PI. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Prescription Drug Promotion (OPDP)  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

Do not submit launch materials until you have received our proposed revisions to the package insert (PI) and patient PI, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>. If you have any questions, call OPDP at 301-796-1200.

If you have any questions, call Lara Akinsanya, Regulatory Project Manager, at (301) 796-9634.

Sincerely,

*{See appended electronic signature page}*

Ann T. Farrell, M.D.  
Division Director  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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ANN T FARRELL  
10/12/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Friday, October 12, 2012 6:55 AM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Oct 12 Clinical Pharmacology- Information Request : NDA 203469/ponatinib DUE 10/16

**Attachments:** LIPASE.xpt; LIPASE\_GR.xpt

Dear Andrew Slugg,

As we need to perform additional analysis on does-intensity-response relationship, please provide the following information for Study AP24523-10-201:

1. Matched dose-intensity for each of the following 3 variables of each subject: LAB\_LIPA, PANC, and AE\_LIPAS for dataset LIPASE.xpt (as attached).
2. Matched dose-intensity for each of the following 3 variables of each subject: AGRADE, LGRADE, and GRADE for dataset LIPASE\_GR.xpt (as attached).
3. Systolic and diastolic blood pressures at baseline, HYPRD6, HYPRD12 and HYPRDAT of each subject for recently provided datasets ader.xpt and ader3.xpt
4. Since the rate of hypertension is different between the ader.xpt and the vital signs dataset, please provide the dose-intensity-hypertension dataset based on vital signs data. The dataset should be in similar format to that of ader.xpt and ader3.xpt. Additionally, also include a column which specifies baseline SBP and DBP for each patient.



LIPASE.xpt (5 KB) LIPASE\_GR.xpt (19 KB)

Please respond to the above Information Request by **Tuesday, October 16, 2012**:

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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MONSURAT O AKINSANYA  
10/12/2012

## Akinsanya, Lara

---

**From:** Akinsanya, Lara  
**Sent:** Friday, October 12, 2012 6:50 AM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Oct 12 Microbiology- Information Request : NDA 203469/ponatinib DUE 10/16

Dear Andrew Slugg,

Please respond to the following CMC/Microbiology Information Request by **Tuesday, October 16**, 2012:

- Include microbial limits at the initial time point as part of the post-approval stability program. Provide an analysis of the (b) (4) table coating process and the coating solution's potential to support microbial growth. Include in the analysis the coating parameters, process duration and historical bioburden data, if available

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
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MONSURAT O AKINSANYA  
10/12/2012



NDA 203469

**INFORMATION REQUEST**

ARIAD Pharmaceuticals, Inc.  
Attention: Andrew Slugg  
Director, Regulatory Affairs  
26 Landsdowne Street  
Cambridge, MA 02139

Dear Mr. Slugg:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ponatinib, Tablets, 15 and 45 mg.

We also refer to your September 27, 2012 and October 1, 2012 submissions.

We are reviewing the chemistry section of your submission and have the following comments and information requests. We request a written response by October 12, 2012, in order to continue our evaluation of your NDA.

**Drug Substance**

1. While the operating target ranges outlined in the process description (S.2.2) are reasonable, the proposed design ranges are not adequately supported by the process development studies. You only have limited DoE studies, which are not sufficient to cover more than (b) (4) proposed design ranges for process parameters. In addition, the use of open ended ranges such as "not more than" and "not less than" are vague and do not provide any information about the operating range used during routine manufacturing. We recommend that you revise (or remove) the Design Ranges in S.2.2, which are not supported by your DoE studies. You also need to define how you will use the Design Ranges during routine manufacturing.
2. Change the acceptance criterion of assay in drug substance specification to (b) (4) % w/w (expressed as ponatinib HCl). Calculation of w/w for ponatinib HCl can be done to cover the variability in (b) (4) content.
3. Change the acceptance criterion for impurity (b) (4) in drug substance specification to (b) (4). Your toxicology studies did not support the proposed acceptance criterion at (b) (4).
4. Propose acceptance criteria of (b) (4) for particle size distribution of drug substance. The first mode of the particle size distribution included the sizes of the primary particles and the second mode included the sizes of the aggregates

and/or larger crystals. Therefore, it is important to control the particle size at (b) (4) to reflect the sizes of the primary particles.

### **Drug Product**

5. Discuss if lot-to-lot variability in excipient properties (e.g. bulk density, particle size, surface area) would have any adverse impact on drug product quality. If there is an adverse impact, provide your control strategy.
6. Commit to continue in-process test to demonstrate adequacy of (b) (4) uniformity and homogeneity (e.g. blend uniformity, stratified testing of core tablets) for commercial manufacture of the drug product.
7. We acknowledge the receipt of a design space with compositional changes for core tablet manufacture. Clarify the regulatory flexibility you are seeking for your compositional design space provided in Table 12 of P. 2 section. We believe that inadequate data were provided to support the design space. For making compositional changes we recommend that you follow the recommendation provided in “Guidance for Industry Immediate Release Solid Oral Dosage Forms Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls, In Vitro Dissolution Testing, and In Vivo Bioequivalence Documentation”.
8. (b) (4)
9. (b) (4)
10. Justify the reason for setting the system suitability criterion for (b) (4) at NMT (b) (4); otherwise, set the (b) (4) acceptance criterion at NMT (b) (4) for the HPLC assay of the dissolution samples.
11. Provide 21CFR citation for individual composition of the container/closure system to assure safety upon food contact. Clarify whether the USP<671> for the bottles was conducted after removal of the inner seal of the closure. If not, conduct and report the results of USP<671> after removal of the inner seal for the bottles. For guidance, see section “G” of the “Guidance for Industry, Container Closure Systems for Packaging Human Drugs and Biologics”.
12. Revise your proposed shelf life from (b) (4) months to 12 months based on 12 months real time stability data since your experience with the regulatory dissolution method is limited at this time.

13. Clarify whether you are proposing to use cartons for bottle configuration during commercial manufacture. If you do, submit the cartons for the bottles.

**Biopharm**

14. The following dissolution acceptance criterion is recommended:  $Q = \frac{(b)}{(4)}\%$  at 30 minutes. This recommendation is based on the mean in-vitro dissolution profiles for all strengths at release and under long term (12 months) stability studies. Revise the dissolution acceptance criterion accordingly and submit an updated sheet of specifications for the drug product.
15. Explain why Lots 260262, 260263, 260265 manufactured at  $\frac{(b)}{(4)}$  failed f2 testing using the proposed regulatory dissolution method.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

*{See appended electronic signature page}*

Nallaperumal Chidambaram, Ph.D.  
Acting Branch Chief, Branch II  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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NALLAPERUM CHIDAMBARAM  
10/05/2012

## Akinsanya, Lara

---

**From:** Akinsanya, Lara  
**Sent:** Friday, October 05, 2012 10:55 AM  
**To:** Andrew P. Slugg  
**Cc:** Bao Le; Akinsanya, Lara  
**Subject:** Oct 5 Clinical- Information Request : NDA 203469/ponatinib DUE 10/9

Dear Andrew Slugg,

Please provide the following information regarding patient A-F (MFR Control number 2012IT000679):

1. Please submit all laboratory results from this patient related to the SAE report (all results during or after ponatinib therapy) and recent baseline results prior to initiation of ponatinib. Include the normal range for the laboratory values.
2. Please perform an evaluation for Hy's law similar to your approach (including graphical presentation of liver function tests over time) in Section 3.1.5.2.5 of your Summary of Clinical Safety.
3. Please submit details on the treatment history for CML. Please also specify the disease phase for this patient.

Please respond to this information request by **Tuesday, October 9**, 2012.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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MONSURAT O AKINSANYA  
10/05/2012

## Akinsanya, Lara

---

**From:** Akinsanya, Lara  
**Sent:** Tuesday, October 02, 2012 12:43 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Oct 2 - Clinical Pharmacology- Information Request : NDA 203469/ponatinib DUE 10/4

Dear Andrew Slugg,

As we explore exposure-safety relationship for ponatinib using ADER.xpt of Study AP24523-10-201 for the 27 AE endpoints and the 2 efficacy points, we need the following information:

1. Please update the ADER.xpt dataset to include hypertension and myelosuppression AEs for Study AP24523-10-201.
2. Please submit similar dataset with Grade  $\geq 3$  AEs for Study AP24523-10-201.

Please respond to this information request by **Thursday, October 4**, 2012.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
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MONSURAT O AKINSANYA  
10/02/2012

**Akinsanya, Lara**

---

**From:** Akinsanya, Lara  
**Sent:** Monday, October 01, 2012 12:38 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Submission Error: NDA 203469 Safety Update

Hi Andrew,

We received your submission and have the following information request:

- Your 120-day safety update submission (NDA 203469 SDN 17 Received 9/28/12) contained raw datasets based on the original data-cut off date of April 26, 2012. Please submit ASAP the raw and analysis datasets based on the cutoff date of July 23, 2012

Thanks

Lara

---

**From:** Andrew P. Slugg [mailto:Andrew.Slugg@ariad.com]  
**Sent:** Friday, September 28, 2012 4:14 PM  
**To:** Akinsanya, Lara  
**Subject:** NDA 203469 Safety Update

Hi Lara,

Just a quick note to let you know the Safety Update for NDA 203469 was submitted as sequence 0019 through the electronic submissions gateway earlier this afternoon.

Regarding the remaining information requests, we are working on the CMC response and expect to submit that response on Monday, and expect to submit a response to today's Clinical Response by Wednesday next week.

Have a great weekend.

Andrew

**Andrew P Slugg**  
Director, Regulatory Affairs  
ARIAD Pharmaceuticals, Inc.  
26 Landsdowne Street  
Cambridge, MA 02139  
*Office: +1 617 503 7097*  
*Mobile: +1 617 710 1840*

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MONSURAT O AKINSANYA  
10/01/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Monday, October 01, 2012 12:41 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Oct 1 Clinical- Information Request : NDA 203469/ponatinib DUE 10/3

Dear Andrew Slugg,

Please provide the following information regarding the 2 cases of fatal acute hepatic failure that you reported in the 120-day safety update report:

1. Please submit the autopsy result for patient (MFR Control Number 2012JP000795, DOB [REDACTED] (b) (6)). A preliminary autopsy result would be acceptable, with the full report to follow. If the autopsy reports are not currently available, please advise when you expect the autopsy reports to become available.
2. Please submit the full safety report for patient (MFR Control Number 2012IT000679, DOB [REDACTED] (b) (6)).

Please respond to this information request by **Wednesday, October 3, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
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MONSURAT O AKINSANYA  
10/01/2012



NDA 203469

**NDA ACKNOWLEDGMENT**

ARIAD Pharmaceuticals Inc.  
Attention: Andrew P. Slugg  
Director, Regulatory Affairs  
26 Landsdowne Street  
Cambridge, MA 02139

Dear Mr. Slugg:

We have received your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Iclusig® (ponatinib) 15 mg and 45 mg tablets for oral use

Date of Application: July 30, 2012

Date of Receipt: September 27, 2012

Our Reference Number: NDA 203469

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on November 26, 2012, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Hematology Products  
5901-B Ammendale Road  
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

Secure email between CDER and applicants is useful for informal communications when confidential information may be included in the message (for example, trade secrets or patient information). If you have not already established secure email with the FDA and would like to set it up, send an email request to [SecureEmail@fda.hhs.gov](mailto:SecureEmail@fda.hhs.gov). Please note that secure email may not be used for formal regulatory submissions to applications.

If you have any questions, call me at (301) 796-9634.

Sincerely,

*{See appended electronic signature page}*

Lara Akinsanya, M.S.  
Regulatory Health Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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/s/  
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MONSURAT O AKINSANYA  
09/28/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Friday, September 28, 2012 8:13 AM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Clinical- Information Request : NDA 203469/ponatinib DUE 10/3

Dear Andrew Slugg,

Please respond to the following Clinical Information Request:

1. Please submit narratives for the following G3-4 AEs related to hepatic toxicity. The clinical team notes that these events were not designated as SAEs and as such did not require narratives at the time of initial NDA submission.

USUBJID	AEDECOD	Maximum AETOXGR
AP24534-10-201-956-004	CYTOLYTIC HEPATITIS	4
AP24534-10-201-509-004	CYTOLYTIC HEPATITIS	3
AP24534-10-201-772-001	HEPATOTOXICITY	3
AP24534-10-201-938-011	LIVER DISORDER	3
AP24534-10-201-938-025	HEPATITIS	3
AP24534-10-201-947-001	HEPATOTOXICITY	3
AP24534-10-201-956-008	CYTOLYTIC HEPATITIS	3
AP24534-10-201-959-008	HEPATOTOXICITY	3

2. What are your plans to evaluate the effects of ponatinib on platelet function? Please discuss.

Reason: Clinical review identified patients who developed hemorrhagic AEs even with platelet counts  $\geq$  50K. Neelakantan et al (Haematologica 2012 Sep;97(9):1444) reported abnormal platelet function assay results in 5 patients who received ponatinib. Another TKI, dasatinib, is known to induce platelet dysfunction *in vitro* (refer to dasatinib USPI).

Please respond to this information request by **Wednesday, October 3, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
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MONSURAT O AKINSANYA  
09/28/2012

**Akinsanya, Lara**

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**From:** Akinsanya, Lara  
**Sent:** Monday, September 24, 2012 9:49 AM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Clinical- Information Request : NDA 203469/ponatinib DUE 09/26

Dear Andrew Slugg,

Please respond to the following Clinical Information Request:

1. Submit narratives for the following SAEs:

SUBJID	SAE
048007	BRAIN OEDEMA
005020	NEOPLASM PROGRESSION
962001	NEOPLASM PROGRESSION

2. Submit an analysis dataset to facilitate the clinical reviewer analysis of BCR-ABL mutations (including non-T315I mutations) detected at study entry for Study 10-201 (PACE trial).

Structure: 1 row per USUBJID

Please include the following columns:

- 2.1. USUBJID
- 2.2. Number of bcr-abl mutations detected at study entry
- 2.3. Flag if patient not evaluable for bcr-abl mutation at study entry
- 2.4. Explanation why patient not evaluable for bcr-abl mutation at study entry
- 2.5. 1 column per bcr-abl mutation detected at study entry (i.e. T315I, V299L, etc.)

3. Please provide a description on how bcr-abl mutations were evaluated at study entry for Study 10-201, specifically on evaluation of non-T315I mutations.

Please respond to this information request by **Wednesday, September 26, 2012**.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
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/s/  
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MONSURAT O AKINSANYA  
09/24/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Thursday, September 20, 2012 4:13 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Clinical Pharmacology - Information Request : NDA 203469/ponatinib DUE 09/25

Dear Andrew Slugg,

Please respond to the following information request:

We note that you use an immunoblot assay to measure both non-phosphorylated and phosphorylated CRKL protein as a PD endpoint in your trial 101; we are unable to locate your validation of this assay. Please provide the location of this information in your application or submit it in within 3 business days. If this method has not been validated please indicate in your response when you intend to validate it.

Please respond to this information request by **Tuesday, September 25**, 2012 or provide the revised PI in the part 2 of your rolling submission.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
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MONSURAT O AKINSANYA  
09/20/2012



NDA 203469

**INFORMATION REQUEST**

ARIAD Pharmaceuticals, Inc.  
Attention: Andrew Slugg  
Sr. CMC Associate, Regulatory Affairs  
26 Landsdowne Street  
Cambridge, MA 02139

Dear Mr. Slugg:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Ponatinib, Tablets, 15 and 45 mg.

We also refer to your July 30, 2012, submission.

We are reviewing the chemistry section of your submission and have the following comments and information requests. We request a written response by October 1, 2012, in order to continue our evaluation of your NDA.

1. Provide complete dissolution profile data (raw data and mean values) from the pivotal clinical and primary stability batches supporting the selection of the dissolution acceptance criterion (i.e., specification-sampling time point and specification value) for your proposed product.
2. In the formulation DoE studies, dissolution was identified as a response variable. However, the proposed dissolution method (Dissolution Method-2) was not used to assess the impact of formulation changes on dissolution. Additionally, the dissolution method used (Dissolution Method-1) is not acceptable because it is not discriminating. Thus, the provided dissolution data cannot be used to support the formulation design space. Moreover, the total percentage of all excipient changes at extremes of the formulation design space is more than (b) (4)%. This percent change is considered a major change which requires additional supporting data beyond dissolution profile comparisons (e.g. BA/BE studies). Discuss how bioequivalence is assured upon the proposed ranges in these excipient levels in your formulation design space. If available, provide the data from an *in vivo* bioequivalence study demonstrating that the formulations manufactured with these ingredients at the following extreme levels are bioequivalent. Additionally, provide the *in vitro* comparative dissolution profile data, using the proposed dissolution method, and similarity f2 values demonstrating that the formulations manufactured with these ingredients at the following levels have similar dissolution rate. If no *in vivo* data are available, the formulation design space should be restricted to changes in

formulations comparable to a Level 2 change under SUPAC (b) (4)

3. In the (b) (4) DoE studies, dissolution was a response variable. However, the proposed dissolution method (Dissolution Method-2) was not used to assess the impact of (b) (4) parameters on dissolution. Additionally, the dissolution method used (Dissolution Method-1) is not acceptable because it is not discriminating. Thus, the provided dissolution data cannot be used to support the (b) (4) design space. In order to support the (b) (4) design space, provide *in vitro* comparative dissolution profile data, using the proposed dissolution method, and f2 similarity values demonstrating that the proposed drug product manufactured with press setting variables at the proposed ranges have similar dissolution rate.

If you have any questions, call Jewell Martin, Regulatory Project Manager, at (301) 796-2072.

Sincerely,

*{See appended electronic signature page}*

Nallaperumal Chidambaram, Ph.D.  
Acting Branch Chief, Branch II  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

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/s/  
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NALLAPERUM CHIDAMBARAM  
09/20/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Monday, September 17, 2012 5:01 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Labeling - Information Request : NDA 203469/ponatinib DUE 09/25

**Attachments:** Ponatinib\_format draft\_PI\_091712.doc

Dear Andrew Slugg,

Please respond to the following information request regarding the PI that was submitted:

- Please look at the attached revised PI (with changes tracked) and make the format changes as requested.



Ponatinib\_format  
draft\_PI\_091...

Please respond to this information request by **Tuesday, September 25**, 2012 or provide the revised PI in the part 2 of your rolling submission.

Thank you

Lara

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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MONSURAT O AKINSANYA  
09/17/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Thursday, September 13, 2012 4:49 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Pharmacology/Toxicology Information Request - NDA 203469/ponatinib DUE SEP 19

Dear Andrew Slugg,

Information is missing in the NDA regarding the biologic activity of the human ponatinib metabolite AP24567 to support the following description found in the Pharmacology Written Summary:

- "AP24567, a minor metabolite of ponatinib in human plasma, inhibited the kinase activity of native and T315I mutant ABL with approximately 3-fold greater potency than ponatinib (b) (4)

Results provided in Table 5 of the paper by Huang, et al.(J. Med. Chem., 2010) are not accompanied by a description of what experiments were conducted, and what materials and methods were used. Submit to the NDA clear descriptions of the experimental materials and methods used to characterize the biologic activity of the AP24567 metabolite provided in the Pharmacology Written Summary of NDA 203469.

Please submit requested information by **Wednesday, September 19, 2012**.

Thank you

Lara Akinsanya

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
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/s/  
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MONSURAT O AKINSANYA  
09/13/2012

## Akinsanya, Lara

---

**From:** Akinsanya, Lara  
**Sent:** Thursday, September 13, 2012 10:44 AM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Follow Up - Clinical Pharmacology Information Request - NDA 203469/ponatinib DUE SEP 19

Dear Andrew Slugg,

Please respond to the following- regarding your response to the Agency dated 09/11/2012 (SDN 7).

1) We find your response to "FDA Request #4" inadequate.

- You state the AP24600 PK data for trial 104 was analyzed at ARIAD using a non-validated method. Please state when you plan to validate this assay.
- Your response "Non-compartmental Pharmacokinetic analyses of AP24600 in plasma from trials 101, 102, and 104 were carried out at ARIAD. No electronic data set was created during the analysis" is unclear as it begs the question of how the summary tables you cite in Report ARP263, Section 3 were developed. Please create and submit separate electronic datasets in sas transport format for AP24600 PK concentration and parameters for each trial using a format similar to the "adpk" and "adpkp" files submitted with your other trial reports.

2) We find your response to "FDA Request #5" inadequate.

- The statement "Data for AP24567 were acquired per the validated method but the data were not reported for this analyte as it was not required for this study" is unclear. Were the concentrations and PK parameters of this metabolite determined for this trial? If so please create and submit a electronic datasets in sas transport format for AP24567 PK concentration and parameters for this trial using a format similar to the "adpk" and "adpkp" files submitted with your other trial reports.

3) We find your response to "FDA Request #6" inadequate.

- Please create and submit electronic datasets in sas transport format for raw data for urine and fecal concentrations of ponatinib and its metabolites for this trial using a format that will provide sufficient information to recreate the summary tables you provide in the trial reports for trials ARP 257 and AP24534-11-104.

Please submit requested information by **Wednesday, September 19, 2012**.

Thank you

Lara Akinsanya

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
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MONSURAT O AKINSANYA  
09/13/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Thursday, September 13, 2012 9:43 AM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Clinical Pharmacology (Pharmacometrics) Information Request - NDA 203469/ponatinib DUE TODAY

Dear Andrew Slugg,

During the review process of ponatinib population PK report, *Population Pharmacokinetic Analysis of Ponatinib Exposure in Healthy Volunteers and Patients with Advanced Chronic Myelogenous Leukemia or other Hematologic Malignancies*, we have some questions and would appreciate your clarification.

- In Appendix 8, named as *Final Model NONMEM Output (Pages 75-102)*, of the population PK report, the final model was terminated due to rounding error (Lines 5-6 in Page 85). Most of the PK estimates in Table 6 (Page 32) are indeed from Appendix 8 (except Theta12 = -88.4% in the appendix, and Theta21=14.9 not reported in Table 6). Please clarify if the parameter estimates of the final model (Table 6 , page 32) are based on the NONMEM output (minimization terminated) presented in Appendix 8. If this is true, please justify why model that did not converge was chosen to be the final population pk model.

Please submit requested information by **COB today**.

Thank you

Lara Akinsanya

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
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/s/  
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MONSURAT O AKINSANYA  
09/13/2012



NDA 203469

**METHODS VALIDATION  
MATERIALS RECEIVED**

Ariad Pharmaceuticals, Inc.  
Attention: Andrew Slugg  
Director, Regulatory Affairs  
526 Landsdowne Street  
Cambridge, MA 02139

Dear Andrew Slugg:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ponatinib tablets and to our August 21, 2012, letter requesting sample materials for methods validation testing.

We acknowledge receipt on September 11, 2012, of the sample materials and documentation that you sent to the Division of Pharmaceutical Analysis (DPA) in St. Louis.

If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy  
MVP Coordinator  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
09/11/2012

## Akinsanya, Lara

---

**From:** Akinsanya, Lara  
**Sent:** Friday, September 07, 2012 1:29 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** NonClinical Information Request - NDA 203469/ponatinib DUE SEP 14

Dear Andrew Slugg,

QAA00193.

- Please provide a Compliance page that is signed and dated by the Study Director.

QAA00121.

- Please provide the date animals were assigned to the study and whether they were naive.
- The quarantine period was shorter than the period identified in the protocol. Please clarify.

QAA00194.

- Please provide the Compliance page and QA Statement, signed and dated by the Study Director and QA representative, respectively.
- Drug was used in the study after the expiration date. Please provide the documentation for a retest date covering the in-life phase completed on July 15, 2009.
- Please provide the date animals were assigned to the study and whether they were naive.
- Monkeys were staggered for dosing; however, details of the staggering process were not included in the report to understand the impact on study procedures. Please provide the information.
- Please provide the correction factor for drug potency; this information was not included in the protocol.

220009232.

- Please provide the Compliance page that is signed and dated by the Study Director.

Please submit requested information by **September 14, 2012**.

Thank you

Lara Akinsanya

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
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MONSURAT O AKINSANYA  
09/07/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Friday, September 07, 2012 1:27 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Clinical Pharmacology Information Request - NDA 203469/ponatinib DUE SEP 14

Dear Andrew Slugg,

- We are unable to locate the raw data files for the ponatinib and metabolite PK parameters from trial 101 derived from the data set "Pkload." Please provide the location of this information in your application or submit it in sas transfer format. Please use a format similar to the "adpkp" files submitted with your other trial reports. In addition, please also include a field in this data set that clearly indicates whether the

(b) (4)

Please submit requested information by **September 14, 2012**.

Thank you

Lara Akinsanya

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
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(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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/s/  
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MONSURAT O AKINSANYA  
09/07/2012

## Akinsanya, Lara

---

**From:** Akinsanya, Lara  
**Sent:** Tuesday, September 04, 2012 11:59 AM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Clinical Pharmacology Information Request - NDA 203469/ponatinib DUE SEP 11

Dear Andrew Slugg,

- Regarding your assay 080348VRM\_ACM\_R1, it appears the Cmax concentrations (0.05 ng/mL) for AP24567 at the 2 through 8 dosages in cycle 1 of the 101 trial were below the LLOQ of this assay (0.1 ng/mL). Please clarify this discrepancy.
- Regarding your assay 110316VRM\_ACM, long term frozen sample stability appears 95 days. Please confirm storage time for samples obtained from trials utilizing this assay.
- Regarding your assay 120081VRM\_ACM, long term frozen sample stability appears 26 days yet this assay was developed to evaluate "archived" samples from completed trials. Please confirm storage time for samples obtained from trials utilizing this assay.
- You state in your biopharmaceutics summary that assay 120081VRM\_ACM was utilized to evaluate the metabolite AP24600 trials 101, 102, and 104 yet we are unable to locate PK summary information in your study reports or the raw data in your dataset folder. Please provide the location of this information in your application or submit it.
- You state in your biopharmaceutics summary that assay 120081VRM\_ACM was utilized to evaluate the metabolite AP24567 in trial 102 yet we are unable to locate PK summary information in your study reports or the raw data in your dataset folder. Please provide the location of this information in your application or submit it.
- We are unable to locate the raw data for urine and fecal concentrations of ponatinib and its metabolites in your dataset folders for trials ARP 257 and AP24534-11-104. Please provide the location of this information in your application or submit it.

Please submit requested information by **September 11, 2012**.

Thank you

Lara Akinsanya

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
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MONSURAT O AKINSANYA  
09/04/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Friday, August 24, 2012 5:21 AM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Clinical Pharmacology Information Request - NDA 203469/ponatinib DUE AUG 27

Dear Andrew Slugg,

- For FDA review of the PopPK study report "Population Pharmacokinetic Analysis of Ponatinib Exposure in Healthy Volunteers and Patients with Advanced Chronic Myelogenous Leukemia or other Hematologic Malignancies", please provide us with the NONMEM control streams for the base model, final model and other relevant intermediate models.

Please submit requested information by **August 27, 2012**.

Thank you

Lara Akinsanya

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
(301) 796-9634 (phone)  
(301) 796-9849 (fax)

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MONSURAT O AKINSANYA  
08/24/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Wednesday, August 22, 2012 4:59 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Clinical Information Request - NDA 203469/ponatinib DUE AUG 29

Dear Andrew Slugg,

### Information Request: Cohort Assignments

1. The clinical review team cannot verify the disease phase for all of the patients with CML in Study-201 based on the screening results. How was CML disease phase (CP, AP, or BP) determined in Study-201? Was it investigator-assessed? If the investigator-assessed CML disease phase was not consistent with the screening results, how did you address this issue?
2. Table 1 lists patients whose CML disease phase classification is not consistent with the Study 10-201 protocol. Please provide justification for your cohort assignments.

**Table 1. Discrepancies in Disease Phase Assignments for Study 10-201**

SUBJID	Sponsor-Assigned Cohort	FDA-Assigned Cohort (as per Study-201 protocol)	Basis
947002	CP-CML	AP-CML	BM blasts 15% BM blasts+pros 30%
938006	AP-CML	CP-CML	Does not meet criteria for AP-CML or BP-CML
947012	AP-CML	CP-CML	
948007	AP-CML	CP-CML	
001001	BP-CML	AP-CML	BM blasts 25%; no extramedullary disease noted on CRF
005003	BP-CML	AP-CML	BM blasts 21%; no extramedullary disease on CRF
008003	BP-CML	AP-CML	BM blasts 18%; no extramedullary disease (other than splenomegaly) noted on CRF
023003	BP-CML	AP-CML	BM blasts 21% (should be $\geq$ 30%); no extramedullary disease noted on CRF.
078001	BP-CML	AP-CML	BM blasts 20%; no extramedullary disease noted on CRF.
011002	BP-CML	Ineligible	Normal BM and PB counts, also Ph-negative
083001	BP-CML	AP-CML	Blasts 10%, platelet count 10K; no extramedullary disease noted on CRF.
508001	BP-CML	CP-CML	Does not meet criteria for BP-CML or AP-CML

959005	BP-CML	AP-CML	Blasts 11%, platelet count 5K; no extramedullary disease noted on CRF.
--------	--------	--------	--

3. The following patients would not have been classified as BP-CML if not for the presence of extramedullary disease (other than hepatosplenomegaly). Please provide documentation (i.e., pathology reports, etc.) of the extramedullary disease (other than hepatosplenomegaly) for the following Study 10-201 patients: 944001, 011011, 058001. We note that patients 011011 and 058011 had normal baseline BM and PB counts, and were also Ph-negative.

4. Thirty eight patients (33 R/I, 4 T315I, 1 ineligible) classified as AP-CML would not have been classified as AP-CML if not for the presence of clonal evolution. What is your definition for clonal evolution? Please provide a summary analysis for clonal evolution for all patients classified as AP-CML.

5. Regarding T315I cohort assignments, the clinical team noted the following discrepancies with regards to T315I screening results. Eighteen patients had a screening value of “T315I Detected” of “N” or “Not Amplified”, but had T315I Percent that ranged from 50% to 100%. All of these patients were assigned in the T315I-positive cohorts (see Table 2, derived by joining ADSL and PG datasets).

Please provide details regarding the “T315I Detected” and “T315I Percent” data. What methods were used to determine these variables?

What was the definition of a positive T315I screening assay result in Study 10-201 that lead to a patient being classified in the T315I positive cohorts?

**Table 2. Discrepancies in T315I Cohort Assignment in Study 10-201**

	USUBJID	COHORTSL	DIAG	VISITNUM	VISIT	PGDTC	PGDY	T315I Detected
1	AP24534-10-201-0 01-002	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2010-11-29	-14	NOT AMPLIFIED
2	AP24534-10-201-0 05-004	AP/T315I+	CML - AP	0	SCREENING	2010-09-22	-1	NOT AMPLIFIED
3	AP24534-10-201-0 05-017	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2010-12-21	-1	NOT AMPLIFIED
4	AP24534-10-201-0 17-010	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2011-03-25	-14	NOT AMPLIFIED
5	AP24534-10-201-0 58-005	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2011-01-19	-6	NOT AMPLIFIED
6	AP24534-10-201-0 58-011	BP, Ph+ ALL/T315I+	CML - BP	0	SCREENING	2011-02-18	-47	NOT AMPLIFIED
	AP24534-10-201-0 58-011	BP, Ph+ ALL/T315I+	CML - BP	0	SCREENING	2011-04-05	-1	NOT AMPLIFIED
7	AP24534-10-201-0 83-010	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2011-06-20	-3	N
8	AP24534-10-201-9 40-001	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2011-04-14	-8	NOT AMPLIFIED
9	AP24534-10-201-9 41-003	CP/T315I+	CML - CP	101.01	CYCLE 1 - DAY 1 - UNSCHEDULED 1	2011-07-27	1	N
10	AP24534-10-201-9 46-002	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2011-05-03	-13	NOT AMPLIFIED
11	AP24534-10-201-9 55-001	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2011-04-14	-22	NOT AMPLIFIED
12	AP24534-10-201-9 56-002	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2011-04-27	-72	NOT AMPLIFIED
	AP24534-10-201-9 56-002	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2011-06-22	-16	N
13	AP24534-10-201-9 57-005	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2011-05-25	-1	N
14	AP24534-10-201-9 59-007	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2011-06-15	-14	N

15	AP24534-10-201-9 59-008	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2011-05-25	-13	N
16	AP24534-10-201-9 59-010	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2011-06-30	-8	N
17	AP24534-10-201-9 61-001	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2011-04-06	-12	NOT AMPLIFIED
18	AP24534-10-201-9 61-002	BP, Ph+ ALL/T315I+	Ph+ ALL	0	SCREENING	2011-04-08	-7	NOT AMPLIFIED

Please submit requested information by **August 29, 2012**.

Thank you

Lara Akinsanya

Lara (Monsurat) Akinsanya, M.S.  
 Regulatory Project Manager  
 Division of Hematology Products  
 Office of Hematology and Oncology Products  
 Center for Drug Evaluation and Research  
 (301) 796-9634 (phone)  
 (301) 796-9849 (fax)

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MONSURAT O AKINSANYA  
08/22/2012



IND 078375  
NDA 203469

**PROPRIETARY NAME REQUEST  
- CONDITIONALLY ACCEPTABLE**

ARIAD Pharmaceuticals, Inc.  
26 Landsdowne Street  
Cambridge, MA 02139

ATTENTION: Andrew Slugg  
Director, Regulatory Affairs

Dear Mr. Slugg:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act; and to your New Drug Application (NDA) dated July 30, 2012, received July 30, 2012, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for Ponatinib Tablets, 15 mg and 45 mg.

We also refer to your March 2, 2012, IND correspondence, received March 2, 2012; and to your August 10, 2012, NDA correspondence, received August 10, 2012, requesting review of your proposed proprietary name, Iclusig. We have completed our review of the proposed proprietary name, Iclusig and have concluded that it is acceptable.

The proposed proprietary name, Iclusig, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and "PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012".)

If **any** of the proposed product characteristics as stated in your August 10, 2012, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

IND 078375  
NDA 203469  
Page 2

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Sue Kang, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-4216. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Lara Akinsanya at (301) 796-9634.

Sincerely,

*{See appended electronic signature page}*

Carol Holquist, RPh  
Director  
Division of Medication Error Prevention and Analysis  
Office of Medication Error Prevention and Risk Management  
Office of Surveillance and Epidemiology  
Center for Drug Evaluation and Research

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KELLIE A TAYLOR on behalf of CAROL A HOLQUIST  
08/21/2012



NDA 203469

**REQUEST FOR METHODS  
VALIDATION MATERIALS**

Ariad Pharmaceuticals, Inc.  
Attention: Andrew Slugg  
Director, Regulatory Affairs  
526 Landsdowne Street  
Cambridge, MA 02139

Dear Andrew Slugg:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Ponatinib tablets, 15 mg and 45 mg.

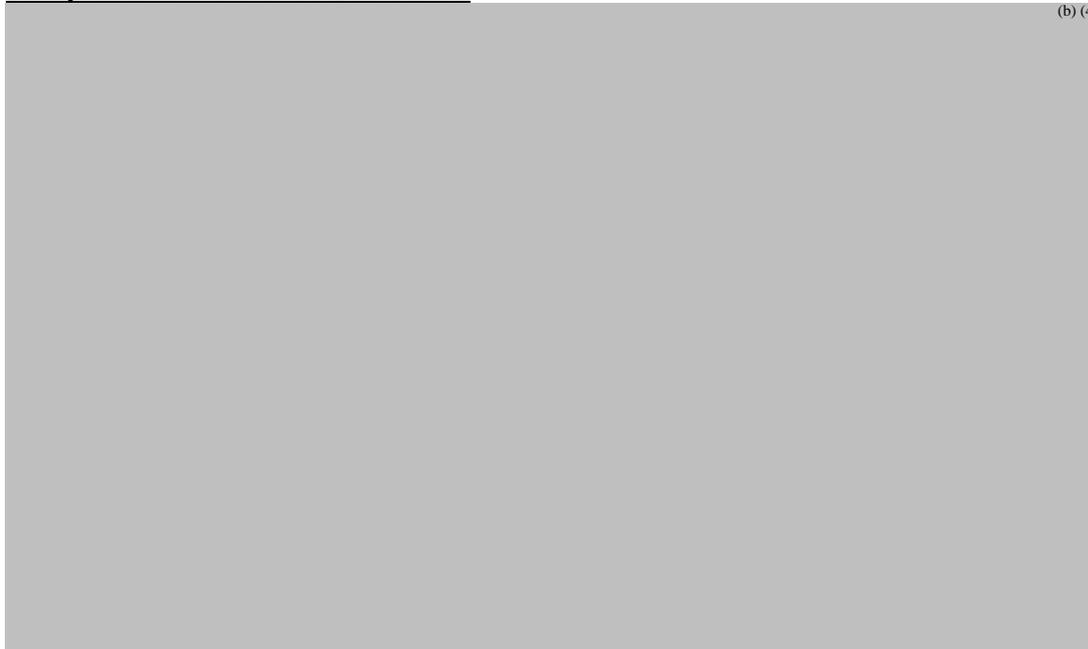
We will be performing methods validation studies on Ponatinib 15 mg tablets, as described in NDA 203469.

In order to perform the necessary testing, we request the following sample materials and equipments:

**Method, current version**

TM0921-00 HPLC Analysis of (b) (4)  
AM-1281 Identification, Content Uniformity, Assay and Impurities Method for Ponatinib  
(AP24534) Tablets, 15 mg and 45 mg

**Samples and Reference Standards**



(b) (4)

Please include the MSDSs and the Certificates of Analysis for the sample and reference materials.

Forward these materials via express or overnight mail to:

Food and Drug Administration  
Division of Pharmaceutical Analysis  
Attn: Michael L. Trehy, Ph.D.  
1114 Market Street, Room 1002  
St. Louis, MO 63101

Please notify me upon receipt of this letter. If you have questions, you may contact me by telephone (314-539-3815), FAX (314-539-2113), or email (Michael.Trehy@fda.hhs.gov).

Sincerely,

*{See appended electronic signature page}*

Michael L. Trehy, Ph.D.  
MVP coordinator  
Division of Pharmaceutical Analysis, HFD-920  
Office of Testing and Research  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

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/s/  
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MICHAEL L TREHY  
08/21/2012

## Akinsanya, Lara

---

**From:** Akinsanya, Lara  
**Sent:** Monday, August 20, 2012 3:28 PM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Clinical Information Request - NDA 203469/ponatinib DUE AUG 27

Dear Andrew Slugg,

### Information Request: AE Datasets

1. In the summary of clinical safety (Section 2.7.4), you mention in 1.1.1.6 that AE terms were recoded to MedDRA v15.0.

- 1.1. Please clarify that the recoding to MedDRA v15.0 refers to the ISS dataset only.
- 1.2. Please confirm that the AE datasets for study 10-201 and 07-101 used the same MedDRA version (13.0 and 11.0 respectively) as described in the study reports.

2. Regarding AE dataset in the ISS, submit a revised AE dataset with the following additional columns for each row in the ISS AE.xpt dataset:

- a. original AEDECOD term
- b. original AESOC term
- c. original MedDRA version
- d. recoded AEDECOD term
- e. recoded AESOC term
- f. recoded MedDRA version
- g. TEAE flag
- h. AETOXGR CTCAE version
- i. Baseline AETOXGR
- j. first dose date
- k. last dose date

3. Regarding ADAE dataset for Study 10-201, the following were noted:

- 3.1. several blank columns (AELLTCD, AEPTCD, AEHLTCD, AEHLGTCD, AEBODSYS, AEBDYSCD)
- 3.2. missing AEDECOD term for 2 AEs (USUBJID AP24534-10-201-029-004 AESEQ 28 and AP24534-10-201-938-019 AESEQ 1)

Submit a revised ADAE dataset for Study 10-201, that addresses 3.1 and 3.2, and add the following columns for each row:

- a. Baseline AETOXGR
- b. last dose date

4. Regarding ADLB dataset for Study 10-201, ADLB dataset contains 20768 rows of which 20731 have a BASEFL="Y". However, raw dataset LB for Study 10-201 contains 223348 rows. Submit a revised ADLB dataset for Study 10-201 with all 223348 lab results. Include a baseline toxicity grade, treatment emergent flag, first dose date, and last dose date for all rows.

Please submit requested information by **August 27, 2012**.

Thank you

Lara Akinsanya

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
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MONSURAT O AKINSANYA  
08/20/2012

## Akinsanya, Lara

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**From:** Akinsanya, Lara  
**Sent:** Friday, August 10, 2012 11:28 AM  
**To:** Andrew P. Slugg  
**Cc:** Akinsanya, Lara  
**Subject:** Clinical Information Request - NDA 203469/ponatinib

Dear Andrew Slugg,

- Refer to your NDA 203469 for the ponatinib drug product. Submit patient data listings for concomitant medications, by clinical investigator site, under Protocol AP24534-10-201 (PACE Trial).

Please submit requested information by **August 15, 2012**.

Thank you

Lara Akinsanya

Lara (Monsurat) Akinsanya, M.S.  
Regulatory Project Manager  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research  
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MONSURAT O AKINSANYA  
08/10/2012



FOOD AND DRUG ADMINISTRATION

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type A meeting  
**Meeting Category:** Pre-NDA/CMC meeting  
**Meeting Date and Time:** June 7, 2012 2012, 12:00 p.m.  
**Meeting Location:** CDER WO 1311  
**Application Number:** IND 078375  
**Product Name:** Ponatinib  
**Indication:** Chronic Myeloid Leukemia  
**Sponsor Name:** ARIAD Pharmaceuticals  
**Meeting Request Date:** May 1, 2012  
**Received Briefing Package** May 10, 2012  
**Meeting Chair:** Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC,  
Clinical Team Leader, Division of Hematology  
Products (DHP)  
**Meeting Recorder:** Mara Miller, Regulatory Project Manger

**FDA ATTENDEES:**

- Ann T. Farrell, M.D., Division Director (Acting), DHP
- Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC, Clinical Team Leader, DHP
- Angelo De Claro, M.D., Medical Officer, DHP
- Janice Brown, Ph.D., CMC Lead, ONDQA
- Amit K. Mitra, Ph.D., CMC Reviewer, ONDQA
- Sandra Suarez, Ph.D., Biopharmaceutics Reviewer, ONDQA
- Kareen Riviere, Ph.D., Biopharmaceutics Reviewer, ONDQA
- Tremel Faison, M.S., Scientific Reviewer, CDRH/OIVD/DIHD
- Mara Miller, M.A., Regulatory Project Manger, DHP

**SPONSOR ATTENDEES:**

- Daniel Bollag, Ph.D., Senior Vice President, Regulatory Affairs and Quality
- Andrew Slugg, Director, Regulatory Affairs
- Frank Haluska, M.D., Ph.D., Senior Vice President, Clinical Research & Development and Chief Medical Officer
- Shirish Hirani, Ph.D., Vice President, Program and Alliance Management
- Timothy Clackson, Ph.D., President, Research and Development and Chief Scientific Officer
- Kristine Nardelli, Senior Manager, Regulatory, Chemistry Manufacturing and Controls
- John Chaber, Ph.D. Senior Director, Analytical Development
- Constance Emmett Associate Director, Quality Control
- Rajesh Mahey, Ph.D. Senior Director, Technical Operations
- Andreas Woppmann, Ph.D. Vice President, Manufacturing Operations
- Christopher Murray, Ph.D., Senior Director, Pharmaceutical Development

**1.0 BACKGROUND**

ARIAD Pharmaceuticals, Inc. requested a Type A meeting request on May 1, 2012, after a CMC meeting held with FDA, to discuss the details of the Phase 3 development program for ponatinib for the indication of patients with newly diagnosed chronic myeloid leukemia in chronic phase. On May 2, FDA granted ARIAD Pharmaceuticals, Inc. meeting request.

On May 31, 2012, FDA emailed ARIAD Pharmaceuticals, Inc. preliminary responses to the question contained in the meeting information package dated May 10, 2012.

**2.0 DISCUSSION**

***Question 1.***

***Ponatinib tablets are manufactured by (b) (4) a contract manufacturer located in (b) (4) The current (b) (4) (b) (4) is in the process of being decommissioned and replaced by the newly commissioned high-containment facility (b) (4) The drug product used to date in the pivotal PACE trial, the ongoing Expanded Access Protocol, and the primary registration stability lots was manufactured at (b) (4)***

*Tablets already manufactured at the (b) (4) facility will be supplied for clinical use shortly, followed by the manufacture of the planned process validation lots and future commercial supply. A proposal to support the site qualification and transfer of manufacture from (b) (4) to (b) (4) was discussed with FDA in a Type C meeting on 27 April 2012. ARIAD and FDA were unable to agree on a specific plan that would allow for the submission of a New Drug Application (NDA) for ponatinib in July 2012, the timeframe discussed at the 16 February 2012 Pre-NDA meeting. ARIAD has developed a plan (see Company Position) that we believe addresses FDA's requests and supports submission of the ponatinib NDA in July 2012.*

*Does the Agency agree that this plan will provide adequate data in the NDA and during the course of the NDA review to support the (b) (4) facility as the commercial manufacturing site for ponatinib?*

**FDA Response: No. Submit in your NDA 3 months accelerated and available long-term stability data for three batches of each strength produced at (b) (4) facilities. In addition, provide multi-point dissolution profile comparisons for your product manufactured at the current and new sites using the following media: 0.1N HCL, pH 4.5 USP buffer, pH 6.8 USP buffer, and water.**

**As previously suggested in the Agency's May 03, 2012 communication, we recommend that you consider a rolling submission for your NDA. The submission can include all modules except the stability update which can be submitted in September-October 2012 when the data becomes available. Please be advised that the review clock does not officially start until the stability update is received. A rolling submission would allow inspections to be scheduled and the review process would be significantly underway by the time the stability update is received.**

**General comments:**

Please be advised that if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity (NME) and the final component of your rolling review submission is received on or after October 1, 2012, the application will be subject to "The Program" under PDUFA V.

For NMEs under the Program (e.g., NMEs submitted after October 1, 2012), during the Pre-NDA meeting, there should be discussion and agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. The FDA and the Applicant may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to

materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission. Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities. Information on PDUFA V and "The Program" is available at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

Please note that if you plan to submit the last component of your rolling review submission prior to October 1, 2012, your application will not be subject to PDUFA V. Please let the Division know whether you plan to submit the last component of your rolling review prior to October 1, 2012 as soon as possible and before this scheduled meeting.

#### **Meeting Discussion:**

**The Agency continues to recommend that ARIAD submit a rolling submission. The review division plans to initiate their reviews upon receipt of a completed section. In addition, it would be most helpful if sites for inspection were submitted in July 2012 and be available for inspection. The Agency recommends that ARIAD submit all available information at the onset of the rolling submission and complete the submission with the stability update and safety update when available, at one time point.**

**The Agency suggested that ARIAD meet with (b) (4) regarding the (b) (4) facility to see if they would be ready for inspection as the launch facility.**

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

No issues identified requiring further discussion.

### **4.0 ACTION ITEMS**

No issues identified requiring further actions.

### **5.0 ATTACHMENTS AND HANDOUTS**

ARIAD's presentation has been attached to the meeting minutes.

Meeting Chair

*{See appended electronic signature page}*

Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC,  
Clinical Team Leader  
Division of Hematology Products  
Office of Hematology and Oncology Products  
Center for Drug Evaluation and Research

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VIRGINIA E KWITKOWSKI  
06/08/2012



FOOD AND DRUG ADMINISTRATION

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B meeting  
**Meeting Category:** Pre-NDA meeting  
**Meeting Date and Time:** February 16, 2012, 2:00 p.m.  
**Meeting Location:** CDER WO 1315  
**Application Number:** IND 078375  
**Product Name:** Ponatinib  
**Indication:** Chronic Myeloid Leukemia  
**Sponsor Name:** ARIAD Pharmaceuticals  
**Meeting Request Date:** October 24, 2011  
**Received Briefing Package** January 4, 2011  
**Meeting Chair:** Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC,  
Clinical Team Leader, Division of Hematology  
Products (DHP)  
**Meeting Recorder:** CDR Diane Hanner, M.P.H., M.S.W.

**FDA ATTENDEES:**

- Edward Kaminskas, M.D., Acting Deputy Director, DHP
- Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC, Clinical Team Leader, DHP
- R. Angelo De Claro, M.D., Medical Officer, DHP.
- Adam George, Pharm.D, Senior Regulatory Management Officer, DHP.
- Kallappa Koti, Ph.D., Mathematical Statistician, DB 5.
- Mark Rothmann, Ph.D, Acting Team Leader, DB 5.
- Brenda Gehrke, Ph.D., Pharmacologist, Acting Supervisory Pharmacologist,  
DHOT
- Stacy Ricci, Ph.D., Pharmacologist/Toxicologist, DHOT (Telephone)
- Young Jin Moon, Ph.D., Clinical Pharmacology Reviewer, DCP5
- Julie Bullock, Pharm.D., Team Leader, Office of Clinical Pharmacology, DCP5

- Lea Carrington, M.S., M.B.A., Reviewer, OIVD/DIHD/CDRH
- Tremel A. Faison, M.S., RAC, SCT (ASCP) OIVD/CDRH (Telephone)
- Jennifer S. Dickey, Ph.D., RAC, OIVD/CDRH
- Elizabeth Mansfield, Ph.D., Team Leader, OIVD/DIHD
- Douglas Warfield, Ph.D., OPI/OBI/DDMSS
- Diane Hanner, M.P.H., M.S.W., Senior Program Management Officer, DHP

**SPONSOR ATTENDEES:**

- Daniel Bollag, Ph.D., Senior Vice President, Regulatory Affairs and Quality
- Andrew Slugg, Director, Regulatory Affairs
- Frank Haluska, M.D., Ph.D Senior Vice President, Clinical Research & Development and Chief Medical Officer
- Christopher Turner, M.D., Medical Director, Clinical Affairs
- Shirish Hirani, Ph.D., Vice President, Program and Alliance Management
- Timothy Clackson, Ph.D., President, Research and Development and Chief Scientific Officer
- Harvey Berger, M.D., Principal Founder, Chairman of the Board and Chief Executive Officer
  
- Maureen Curran, R.N., B.S.N., Senior Director, Drug Safety and Pharmacovigilance
  
- Ruth O'Halloran, Ph.D., Associate Director, Medical Writing
- (b) (4)
  
- Stephanie Lustgarten Ph.D., Associate Director, Biostatistics
  
- Kristine Nardelli, Senior Associate, Regulatory Chemistry Manufacturing and Controls
  
- (b) (4)

**1.0 BACKGROUND**

ARIAD Pharmaceuticals, Inc. requested a Pre-NDA meeting with FDA on

October 24, 2011, to discuss the details of the Phase 3 development program for ponatinib for the indication of patients with newly diagnosed chronic myeloid leukemia in chronic phase. On November 1, 2011, FDA granted ARIAD Pharmaceuticals, Inc. meeting request.

Ponatinib is a synthetic, orally-active tyrosine kinase inhibitor. Ponatinib was designed to inhibit native BCR-ABL, as well as mutated forms of the protein that cause resistance, including T315I.

On February 2, 2012, FDA emailed ARIAD Pharmaceuticals, Inc. preliminary responses to the questions contained in the meeting information package dated January 4, 2011.

## 2.0 DISCUSSION

### Question 1

The clinical pharmacology package for ponatinib in support of registration will include non-compartmental pharmacokinetic (PK) data for 81 patients with single-dose and steady state data and data from 3 healthy subject clinical pharmacology studies. An integrated population PK analysis will allow for development of a compartmental PK model and subsequent evaluation of intrinsic and extrinsic sources of variability in ponatinib PK behavior. The effect of food on ponatinib absorption is currently being evaluated. The ongoing ketoconazole drug interaction study will clarify the relative importance of CYP3A4/5 towards the overall elimination of ponatinib in humans. The ongoing human ADME study will inform us about the relative importance of hepatic and renal elimination processes for overall ponatinib clearance. A previously submitted analysis of the QTc intervals of patients who received ponatinib 30 mg or higher in the Phase 1 clinical trial revealed there was no significant effect of ponatinib on cardiac repolarization, obviating the need for a separate dedicated QTc study.

Does the Agency agree that the clinical pharmacology program is adequate for the proposed registration package of ponatinib in the proposed indication?

**FDA Response: The adequacy of the clinical pharmacology program to support the marketing application will be a review issue. Submit the protocols for the three clinical pharmacology studies (rifampicin interaction study, lansoprazole study, and the hepatic impairment study) you plan to conduct post-approval to the IND for agency review and concurrence. These studies should ongoing by the time the NDA is submitted.**

**In addition, please see the attached Question Based Review (QBR) format and include this information in section 2.7.2 of your eCTD NDA submission with appropriate links to relevant study reports and analyses used to support your responses.**

**The data from study AP24534-07-101 appear reasonable to exclude large QTC effects with Ponatinib. However, whether or not 60 mg q.d. covers the high exposure clinical scenario will depend on the results of the studies evaluating the effect of**

IND 078375 (Ponatinib)

**food, organ impairment or administration of CYP3A4 inhibitors on ponatinib PK. Provide ECGs and adverse event data as part of the NDA submission. The final decision on whether a separate dedicated QT study is needed will be made after review of all the available data.**

**You should conduct central tendency analysis and categorical analysis and submit it to the FDA in a Cardiac Safety Report format**

- **Central tendency analysis is to provide summary statistics for mean HR, QTc, PR, and QRS interval (together with its 90% two sided confidence interval) change from baseline stratified by different time points.**
  - **Categorical analysis which typically includes number and percentage of subjects with**
  - **Absolute QT/QTc values > 450 ms, >480 ms, and >500 ms; as well as change from baseline > 30 ms and > 60 ms.**
  - **PR changes from baseline  $\geq$  25% and absolute value over > 200 ms.**
  - **QRS changes from baseline  $\geq$  25% and absolute value over > 110 ms.**
  - **Abnormal ECG findings**
  - **HR < 60 bpm, > 100 bpm**
- **AEs that could be associated with prolongation of cardiac repolarization or proarrhythmia e.g., palpitations, dizziness, syncope, cardiac arrhythmias, and sudden death.**

**ARIAD Reply:**

Planned Clinical Pharmacology Studies:

ARIAD will submit protocols for the rifampicin interaction study, lansoprazole study, and hepatic impairment study to IND 078375 for agency review prior to submission of the NDA. ARIAD believes that submission of these protocols prior to the submission of the NDA will fulfill FDA's request that these trials be ongoing.

**Meeting Discussion: The Agency reiterated that the three studies should be ongoing at the time of NDA submission. At a minimum, the clinical trial sites should be identified and final protocols under review by IRB.**

**Question 2**

The ponatinib NDA will include 2 prospective clinical trials in leukemia patients: a pivotal phase 2 trial of ponatinib in patients with CML or Ph+ ALL who are resistant or intolerant to either dasatinib or nilotinib or patients with the T315I mutation (AP24534-10-201, also known as the PACE trial); supported with a phase 1 dose escalation trial to determine the safety, tolerability and maximum tolerated dose of ponatinib in patients with  <sup>(b) (4)</sup> advanced CML and other hematologic malignancies (AP24534-07-101). The Clinical Study Reports (CSRs) for both trials will present efficacy data based on planned analyses detailed in the study protocol and/or statistical analysis plan. The efficacy data from both studies will not be pooled. However, to facilitate comparison of results between studies, side-by-side presentations of efficacy data will be provided in the

Clinical Summary of Efficacy (2.7.3). An overview of the planned presentation of efficacy data as they will be presented in the NDA is provided in the company position.

Does the Agency agree with the proposed approach to the presentation of ponatinib efficacy data?

**FDA Response: No. We disagree with the definition of the analysis population for efficacy analysis. The Agency recommends that the efficacy population be defined as all patients who were registered to the clinical trial (ITT population), regardless of receiving a dose. Analysis based on the treated population or per protocol population may be presented as sensitivity analyses. You should provide at least 6-months follow-up data for all patients in the PACE trial.**

**Include data on prior therapies received for all patients, including complete documentation of resistance, intolerance, or both, to prior anti-CML treatments.**

**Please plan to discuss why you have excluded from the “intolerant” population, those who achieved CCyR (CP-CML) or MaHR (AP, BP). The definition of intolerance will be a review issue.**

**Your proposal to present side-by-side comparison of the PACE trial and AP24534-07-101 in the Clinical Summary of Efficacy is acceptable.**

**Because your application is based on a single pivotal trial (PACE trial), an Integrated Summary of Efficacy (ISE) is not needed.**

**ARIAD Reply:**

Population for Efficacy Analysis:

ARIAD believes that the “treated” population defined in the pivotal phase 2 trial protocol (section 19.2.1) and statistical analysis plan (section 3.2 ) is aligned with the Agency’s concept of an intent-to-treat analysis as it includes all patients who have been enrolled in the trial. Section 6 of the protocol specifies that in order to be enrolled, a patient must initiate study treatment (an enrolled patient is defined as “a patient who has signed the informed consent form, completed all screening evaluations, has been deemed eligible for the trial and for whom the enrollment procedure has been completed, and received first dose of ponatinib”). As this is a single-arm trial, the “treated” population is an appropriate population for efficacy analysis consistent with the protocol.

Including patients who did not receive treatment, did not meet the enrollment criteria, and who were otherwise not required to be followed by the protocol would likely yield results that would be difficult to interpret and of limited utility in assessing the efficacy of ponatinib. Moreover, this would present a different population than that being analyzed for safety and would therefore confound the overall risk-benefit assessment of the drug.

ARIAD’s proposed approach is consistent with recent approvals granted to oncology compounds on the basis of single-arm trials. For example, the primary efficacy analysis of the pivotal, single-arm, phase 2 trial that supported registration of the ALK inhibitor crizotinib was conducted on a “response-evaluable” population, which included those

patients who were enrolled and received at least one dose of drug. Conceptually, this is equivalent to the “treated” population we intend to evaluate.

Definition of Intolerance:

At the End of Phase 1 meeting (14 May 2010) ARIAD received the following feedback from FDA on the proposed definitions for resistance or intolerance to dasatinib or nilotinib “The criteria for resistance to or intolerance of nilotinib and dasatinib appear to be acceptable except for grade 3 or 4 hematologic toxicity as criteria for intolerance of dasatinib or nilotinib.” ARIAD subsequently revised the protocol definition of intolerance from:



to

“Patients with grade 3 or 4 toxicity (absolute neutrophil count [ANC] or platelets) while on therapy that is recurrent after dose reduction to the lowest doses recommended by manufacturer (80 mg daily [QD] for dasatinib; 400 mg QD for nilotinib) in the absence of a CCyR for CP patients or MaHR for AP, BP or Ph+ ALL patients.”

ARIAD believes that the resulting definition for intolerance to dasatinib or nilotinib is in keeping with FDA’s previous feedback and with the approved uses of dasatinib and nilotinib and is therefore appropriate.

**Meeting Discussion: The definition of the primary analysis populations will be a review issue. The Agency recommends that the sponsor submit the efficacy and the safety data from the 449 patients enrolled in the PACE trial.**

**The Agency explained that a broader definition of intolerance would have also been acceptable; i.e., patients with intolerance regardless of response.**

**Addendum: The Agency recommended that the Sponsor submit CONSORT flow diagrams that detail the disposition of each patient in the PACE trial, including screening failures.**

**Question 3**

In the pivotal phase 2 trial, AP24534-10-201, a protocol amendment was implemented that allowed for a larger sample size to facilitate enrollment of the T315I cohorts. The protocol amendment specified that the primary analysis will be based on all patients

IND 078375 (Ponatinib)

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enrolled in each of the 6 cohorts, which will provide for the most robust estimates of MCyR rate and MaHR rate. In accordance with the pre-specified statistical analysis plan (SAP), in the event of over-enrollment beyond 10% of the original plan, a sensitivity analysis will be performed on the planned sample size for each cohort.

Does the Agency agree with the proposed plan for handling analysis of the larger than originally planned number of patients in the pivotal phase 2 trial?

**FDA Response: Yes.**

**ARIAD Reply:**

No discussion necessary.

#### **Question 4**

In support of the NDA, ARIAD is planning a review of all available safety information on ponatinib. Clinical Study Reports (CSRs) will present safety analyses from individual trials. An Integrated Summary of Safety will include pooled presentation of safety data from the phase 1 and phase 2 clinical trials. Safety data including adverse events from healthy volunteers enrolled in clinical pharmacology studies will be presented separately. Line-listings of serious adverse events from compassionate use and investigator-sponsored trials will be presented separately. An overview of the planned presentation of safety data as they will be presented in the NDA Summary of Clinical Safety (2.7.4) and the Integrated Summary of Safety (5.3.5.3) is provided in the company position.

Does the Agency agree with the proposed approach to presentation of the ponatinib safety data as described?

**FDA Response: Yes. However, you should note the following:**

**You are required to submit a safety update as per 21 CFR 314.50(d)(5)(vi)(b).**

**Adverse events with no end dates will be assumed as ongoing or unresolved adverse events. A high number of unresolved adverse events (e.g.,  $\geq$  Grade 2, serious AEs) would affect the overall risk-benefit assessment. We encourage you to capture adequate follow-up data for all adverse events.**

**Include the MedDRA hierarchy (SOC, HLT, HLTG, PT) and 8-digit MedDRA code for all adverse events. The ISS should use the same version of MedDRA and NCI-CTC grading systems.**

**Include verbatim terms for all adverse events. Submit a coding dictionary that maps each verbatim term to the MedDRA coded term.**

**Because your application is based on a single-arm clinical trial, the labeling for adverse events should be regardless of attribution or relatedness.**

**Given the safety reports for G3-4 transaminase elevation, conduct an analysis for Hy's law cases and submit with the NDA.**

**ARIAD Reply:**

No discussion necessary.

### Question 5

ARIAD proposes to provide case report forms (CRFs) and patient narratives for patient deaths occurring within 30 days of last dose of study drug, as well as serious adverse events and withdrawals due to adverse events from the pivotal phase 2 trial (AP24534-10-201), the supporting phase 1 trial (AP24534-07-101), and from the clinical pharmacology clinical studies.

Does the Agency concur with the proposal for inclusion of the specified CRFs and patient narratives in the NDA?

**FDA Response: Yes. However, you should be prepared to submit additional case report forms (CRFs) upon request.**

### ARIAD Reply:

No discussion necessary.

### Question 6

SAS files will be submitted to accompany the NDA submission documents. SAS files from the phase 1 trial will be submitted as SAS Version 5 transport original formatted data. SAS files from the phase 2 trial will be submitted in study data tabulation model (SDTM) format. SAS files from the Integrated Summary of Safety (ISS) will be submitted in SDTM format.

Does the Agency agree with the proposed plan for submission of SAS files to accompany the submission?

**FDA Response: No. You are required to submit raw and analysis datasets for all clinical trials (including clinical pharmacology) included in the NDA.**

- **In the appropriate clinical pharmacology sections of the eCTD include the following: Datasets for clinical pharmacology and biopharmaceutics studies should be complete and not be limited to PK/PD. For example, domains related to safety (e.g., ADR's), demographics, non-PK laboratory values, concomitant drug use should be included. All of these are important in identifying patterns of potential clinical pharmacology related causes of clinical safety outcomes.**
- **Provide all concentration-time and derived PK parameter datasets for all studies. In the study reports, present the PK parameter data as geometric mean with coefficient of variation (and mean  $\pm$  standard deviation) and median with range as appropriate.**
- **Provide a table listing of patients with renal or hepatic impairment who have received ponatinib, organized by trial number. Include available renal and hepatic function parameters such as SCr, CLCr calculated by the Cockcroft Gault equation (or eGFR calculated by MDRD), AST/ALT, T.Bili, platelet count, etc for each patient in the listing. Also, provide summaries of the**

**following information for each patient: PK and PD data, safety, and clinical efficacy.**

- **We encourage you to refer to the following pharmacometric data and models submission guidelines (<http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm180482.htm>). For any population PK models all datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been excluded from the analysis should be flagged and maintained in the datasets. Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt). A model development decision tree and/or table which gives an overview of modeling steps. For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.**

**Please note that define.xml must be included for CDISC datasets, and the .pdf should be submitted in addition to ease the review process. Also, please refer to the Study Data Specifications for folder structure and content details.**

**See also the additional comments.**

**ARIAD Reply:**

No discussion necessary.

**Question 7**

Our original NDA dossier will be submitted for accelerated approval. If the data package is sufficiently strong, 2-year follow-up data from PACE should be adequate to support full approval. If the data package is not sufficiently strong for eventual conversion to full approval, a successful separate randomized trial vs. imatinib in newly diagnosed patients should be an adequate confirmatory trial to support full approval. Does the Agency agree?

**FDA Response: The Agency reminds you that accelerated approval requires demonstration of meaningful therapeutic benefit over available therapy, or absence of available therapy. Determination of available therapy is made at the time of regulatory action.**

IND 078375 (Ponatinib)

**Because the T315I cohort may not have received all 3 TKIs with regular approval for resistant/intolerant CML, you should provide justification (e.g., non-clinical data, literature reports) that patients with T315I-mutant CML have no available therapy.**

**ARIAD Reply:**

No discussion necessary.

**Question 8**

At the End of Phase 1 Meeting, the Agency recommended that an in vitro diagnostic be developed for marketing approval to support the approval of ponatinib in patients with a T315I mutation. (b) (4)

(b) (4)

**FDA Response:** We recommend that (b) (4)

(b) (4)

**ARIAD Reply:**

No discussion necessary.

**Additional comments:**

- 1. The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis should be included in the NDA submission.**
- 2. Please provide the location of the SAS dataset, the names of the variables used and the programs used to get every value that will be appearing in the label.**
- 3. All manufacturing and clinical trial sites must be ready for inspection at the time of NDA submission.**
- 4. We note that you have not proposed a proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a request for a proposed proprietary name review. (See the Guidance for Industry, *Contents of a Complete Submission for the Evaluation of Proprietary Names*, <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf> and “PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2008 through 2012”.)**

**3.0 ISSUES REQUIRING FURTHER DISCUSSION**

No issues identified requiring further discussion.

#### **4.0 ACTION ITEMS**

No issues identified requiring further actions.

#### **5.0 ATTACHMENTS AND HANDOUTS**

ARIAD's presentation has been attached to the meeting minutes.

Meeting Chair

*{See appended electronic signature page}*

Virginia Kwitkowski, M.S., R.N., A.C.N.P.-BC,  
Clinical Team Leader, DHP

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VIRGINIA E KWITKOWSKI  
02/21/2012



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

IND 078375

**MEETING MINUTES**

Ariad Pharmaceuticals, Inc.  
Attention: Carol Young  
Manager, Regulatory Affairs  
26 Landsdowne Street  
Cambridge, MA 02139-4234

Dear Ms Young:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AP24534.

We also refer to the telecon between representatives of your firm and the FDA on February 10, 2011. The purpose of the meeting was to discuss manufacturing development plans for preparation of a marketing application for ponatinib in 2H12 based on the results of the ongoing Phase 2 pivotal clinical trial.

A copy of the official minutes of the telecon is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Tu-Van Lambert, Product Quality Regulatory Health Project Manager, at (301) 796-4246.

Sincerely,

*{See appended electronic signature page}*

Sarah Pope Miksinski, Ph.D.  
Chief, Branch II  
Division of New Drug Quality Assessment I  
Office of New Drug Quality Assessment  
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



**FOOD AND DRUG ADMINISTRATION**  
**CENTER FOR DRUG EVALUATION AND RESEARCH**

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**MEMORANDUM OF MEETING MINUTES**

**Meeting Type:** Type B  
**Meeting Category:** End of Phase 2

**Meeting Date and Time:** Thursday, February 10, 2011  
**Meeting Location:** Teleconference

**Application Number:** IND 078375  
**Product Name:** AP24534 (ponatinib)  
**Indication:** for treatment of adults with chronic, accelerated or blast phase chronic myelogenous leukemia (CML) or Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) who are resistant or intolerant to either dasatinib or nilotinib. Ponatinib is also indicated for treatment of adult patients with CML or Ph+ ALL who have a T315I BCR-ABL mutation.

**Sponsor/Applicant Name:** Ariad Pharmaceuticals, Inc.

**Meeting Chair:** Sarah Pope Miksinski, Ph.D.  
**Meeting Recorder:** Tu-Van L. Lambert, M.S.

**FDA ATTENDEES**

Sarah Pope Miksinski, Ph.D. – Chief, Branch II, Office of New Drug Quality Assessment (ONDQA), Division of New Drug Quality Assessment I (DNDQA I)  
Janice T. Brown – CMC Lead, ONDQA, DNDQA I  
Sharmista Chatterjee, Ph.D. – Product Quality Reviewer, ONDQA, DNDQA I  
Joyce Z. Crich, Ph.D. – Product Quality Reviewer, ONDQA, DNDQA I  
Angelica Dorantes, Ph.D. – Biopharmaceutics Team Leader, ONDQA  
Tu-Van L. Lambert – Product Quality Regulatory Project Manager, ONDQA

**SPONSOR ATTENDEES**

Daniel Bollag, Ph.D. - Senior Vice President, Regulatory Affairs and Quality  
John Chaber, Ph.D. - Senior Director, Analytical Development  
Constance Emmett - Associate Director, Quality Control  
Shirish Hirani, Ph.D. - Vice President Program and Alliance Management  
John D. Iuliucci, Ph.D. - Senior Vice President, Development  
Chris Murray, Ph.D. - Senior Director, Manufacturing  
Rajesh Mahey, Ph.D. - Senior Director, Technical Operations  
Kristine Nardelli - Senior Associate, CMC Regulatory Affairs

Meeting Minutes  
Type B  
February 10, 2011

Office of New Drug Quality Assessment

Leonard W. Rozamus - Director, Chemical and Process Development  
Andreas Woppmann, Ph.D - Vice President, Manufacturing Operations  
Carol Young - Manager Regulatory Affairs

## 1.0 BACKGROUND

AP24534 (ponatinib), a novel synthetic orally-active multi-target tyrosine kinase inhibitor, inhibits with high potency and broad specificity BCR-ABL, an abnormal tyrosine kinase that is hallmark of CML and Ph+ALL. Under advice of the Agency, the Sponsor has moved directly from the Phase I to a pivotal Phase 2 trial. The Sponsor expects to complete the trial to support an application in 2Q2012.

The purpose of the requested CMC meeting is to discuss the manufacturing development plans for preparation of a marketing application for ponatinib in 2H12 based on the results of the ongoing Phase 2 pivotal clinical trial. The objectives of the meeting are:

- (1) to discuss details of the Sponsor's CMC development plans for the drug substance and drug product in preparation for the marketing application in 2H12 and commercialization; and
- (2) to seek advice related to specific aspects of the CMC development program leading to product registration.

In this meeting, the Sponsor requests additional clarification and comments on the CMC development program to further develop the IND towards an NDA submission.

## 2. DISCUSSION

Preliminary meeting comments were issued on February 8, 2011. Based on review of the preliminary comments, the Sponsor requested further discussion to clarify information for all questions and comments. Sponsor questions are indicated in ***Bold Italics*** font, Agency preliminary comments are in Regular font, and further meeting discussion is indicated in *Italics* font.

### QUESTION 1

***The synthesis of the drug substance is outlined in Figure 10.1-1. Based on the currently available data, ARIAD anticipates that the proposed starting materials will be*** (b) (4)

(b) (4)

***Does the Agency agree with this approach for Regulatory Starting Materials?***

### Agency Response

There is insufficient information in the meeting package to comment at this time on the suitability of (b) (4) as regulatory starting materials. Based on your meeting package, FDA does not agree with the designation of (b) (4) as a regulatory starting material due to the propinquity to the final drug substance. The final determination will be made during NDA review process based on the totality of the provided data.

In your NDA submission, provide the following information for the future proposed starting materials:

- Full supplier information from the intended vendors of the proposed starting materials.
- Appropriate controls of the proposed starting materials using validated analytical test methods to separate and measure potential impurities.
- In-house acceptance criteria and Vendor's Certificate of Analysis
- Description of synthetic scheme and methods of manufacture
- Impurity profile
- Thorough discussion of potential carry-over of impurities that are present in the starting materials to the final drug substance, based on analytical data.
- Detailed discussion (including data) on purging studies using impurities to demonstrate the ability of the manufacturing process to remove and control the impurities to desired levels.
- Change control strategies for any potential revisions to the manufacture of the proposed starting materials, including the proposed procedures for the vendor's reporting of any changes in starting material manufacture to you.
- Supportive literature data, as available.
- Validated analytical methods capable of resolving and quantifying impurities in the drug substance that are carried over from the proposed starting materials and the process impurities that result in the synthesis of the drug substance from the proposed starting materials.
- Complete information supporting purified and well-characterized referenced starting materials.
- Purging studies that demonstrate that the proposed starting materials and the impurities in the proposed starting materials will not be present at levels greater than (b) (4) in the drug substance, provided these compounds are nonstructural alerts for genotoxicity.
- If any of the above materials are structural alerts for genotoxicity, they may have to be limited to much lower levels than (b) (4) such that the total daily intake of such impurities based on the maximum daily dose does not exceed the Threshold for Toxicological Concern (TTC). Alternatively, the proposed levels may be qualified for genotoxicity.

### **Discussion**

*The Sponsor requested clarification on the proposed starting material (b) (4). In general the Agency does not agree with this as the starting material due to its propinquity to the drug substance. The Sponsor requested that this issue be revised at a later time when more experience and data with this synthetic route become available. The Agency confirmed that the discussion can be pursued at a later time but also confirmed that the recommendation will, most likely, not be changed.*

### **QUESTION 2**

*Current drug substance specifications are presented below in Table 10.2-1. These specifications have been developed to confirm and ensure the quality and consistency of the drug substance, AP24534 HCl, and are reflective of the manufacturing experience to date. As additional manufacturing experience is gained at the intended commercial scale and at the*

*expected commercial manufacturing site, ARIAD will re-evaluate drug substance specifications prior to submission of a marketing application, including the following:*

- *Numerical limits will be assigned to the specifications that are currently “report results.”*
- *Limits (weight percent) will be added for specified and unspecified impurities consistent with ICH guidelines and manufacturing experience.*
- *Where applicable, specifications and limits will conform to United States Pharmacopeia-National Formulary and the European Pharmacopeia.*

*Does the Agency agree with this approach for development of commercial drug substance specifications?*

#### **Agency Response**

Your general approach for development of commercial drug substance specifications appears reasonable. Suitable limits should be established based on manufacturing experience, stability data, and safety considerations. Additionally, justify your proposed acceptance criteria for Assay. The Agency does not agree with your proposal to implement (b) (4) for microbial limits and particle size testing. The final determination of acceptability of the drug substance specification will be made during NDA review process based on the totality of the provided data.

In order to evaluate your proposed (b) (4) acceptance criteria for (b) (4) (b) (4) please provide a summary indicating levels that were administered to patients on a mg/kg basis in the phase 1 trials. Please also provide the number of patients exposed to different levels of (b) (4)

#### **Discussion**

*The Sponsor agreed to provide all information including the justification for the assay acceptance criterion and the proposed removal of particle size testing and microbial limits testing in the drug substance specifications in the NDA (Please refer to Slides 6 & 7 of the presentation materials). The Agency also stated that, in order to justify the removal of particle size and microbial limits testing, AP24534 batch data for these attributes should be collected throughout development and submitted in the NDA.*

*The Agency requested clarification regarding the Sponsor’s question as it was unclear whether the question applied to ongoing IND or the NDA. The Sponsor confirmed that the intention of the question was applied to the IND stage. The Agency stated that the initial response applied to the NDA and requested that the Sponsor submit an amendment with supporting information for the proposed acceptance criterion for (b) (4) including batch data, method quantitation, etc. The Sponsor agreed to confirm that the proposed acceptance criterion for (b) (4) is not a recent change for the IND. Also see Post Meeting Comments.*

#### **QUESTION 3**

***ARIAD's approach and experience in the development and manufacture of the drug product, the AP24534 tablet (ponatinib), a debossed, film-coated immediate release tablet for once daily oral administration, are described below. The process flow for manufacture of the drug product is outlined in Figure 10.3-1. Conventional pharmaceutical excipients are used in the formulation of the AP24534 Tablet. The drug product manufacturing process is being transferred from its current clinical development and manufacturing site to the expected commercial contract manufacturer. Product lots from the expected commercial manufacturer will also serve as clinical supply for the Phase 2 pivotal clinical trial that is currently ongoing. ARIAD plans to compare the product lots from the clinical and expected commercial manufacturing sites based on the following:***

- ***Comparison of the release testing results for the multi-point dissolution profiles at (b) (4) (b) (4) minutes in the USP pH 1.7 hydrochloric acid buffer medium from current and new site showing similarity.***
- ***Accelerated and long-term stability data on 3 lots per strength with 12 months data at time of filing.***

***Does the Agency agree with this approach for comparability testing of product lots from the clinical and expected commercial manufacturing sites?***

**Agency Response**

Your approach is reasonable provided there are no formulation changes in the drug product.

The proposed dissolution testing approach (*comparison of the dissolution profiles in pH 1.7 HCl medium*) supporting the similarity of the product manufactured at the current clinical manufacturing site at (b) (4), to the product to-be-manufactured at the expected commercial site appears to be adequate. However, please note that the dissolution method is product specific. Thus, if your proposed dissolution test has not been approved by the Agency, to support the manufacturing site change you will need to provide dissolution profile comparison data and f2 values in three different dissolution media (pH 1.2, 4.5, and 6.8) using the same dissolution testing conditions. Refer to "Guidance for Industry - Immediate Release Solid Oral Dosage Forms Scale-Up and Post-approval Changes: Chemistry, Manufacturing, and Controls, *In Vitro* Dissolution Testing, and *In Vivo* Bioequivalence Documentation"

In the NDA submission, provide a minimum of 12 months long term and six months accelerated stability data from three primary batches per strength (both 15 mg and 45 mg) of drug product AP24534 HCl.

**Discussion**

*With regard to the dissolution testing, the Sponsor clarified that that the solubility of the drug at pH 4.6 and 6.8 is very low and therefore, it would not be possible to collect dissolution data in these media. The Agency responded that the Sponsor could provide a justification for not evaluating the dissolution at the higher pH media. However, if the proposed dissolution method is approved during the IND, a justification for no conducting the evaluation in the higher pH media is not longer needed. The Agency recommended*

*submitting to the IND the dissolution method development report for review and comments. The Sponsor committed to submitting this information within a month, and the Agency acknowledged this.*

#### **QUESTION 4**

***Current drug product specifications are presented below in Table 10.4-1. These specifications have been developed to confirm and ensure the quality and consistency of the AP24534 Tablets (ponatinib). As additional manufacturing experience is gained at larger scale and at the expected commercial contract manufacturer, ARIAD will re-evaluate drug product specifications prior to submission of a marketing application, including the following:***

- ***Numerical limits will be assigned to the specifications that are currently “report results.”***
- ***The HPLC test to identify AP24534 in the drug product will be supplemented with an IR spectroscopic test.***
- ***Limits (weight percent) will be added for specified and unspecified impurities consistent with ICH guidelines, manufacturing experience and product stability.***
- ***Where applicable, specifications and limits will conform to United States Pharmacopeia-National Formulary and the European Pharmacopeia.***

***Does the Agency agree with this approach for development of commercial drug product specifications?***

#### **Agency Response**

Your general approach for development of commercial drug product specifications appears reasonable. Suitable limits should be established based on manufacturing experience, stability data, and safety considerations. The Agency does not agree with your proposal to implement (b) (4) for microbial limits and particle size testing.

With respect to the proposed dissolution acceptance criterion of  $Q = \frac{(b)}{(4)}\%$  at (b) (4) minutes for your product, please provide the complete dissolution profile data from clinical and primary (registration) stability batches supporting the proposed specification-time point and specification-value.

Additionally, we have the following comments regarding the dissolution information that should be provided in your NDA.

1. **Dissolution Test:** Include the dissolution method report supporting the selection of the proposed dissolution test. The dissolution report should include the following information:
  - a. solubility data for the drug substance covering the pH range;

- b. detailed description of the dissolution test being proposed for the evaluation of your product and the developmental parameters (*i.e., selection of the equipment/apparatus, in vitro dissolution/release media, agitation/rotation speed, pH, assay, sink conditions, etc.*) used to select the proposed dissolution method as the optimal test for your product. If a surfactant was used, include the data supporting the selection of the type and amount of surfactant. The testing conditions used for each test should be clearly specified. The dissolution profile should be complete and cover at least  $\frac{(b)}{(4)}$ % of drug release of the label amount or whenever a plateau (*i.e., no increase over 3 consecutive time-points*) is reached. We recommend use of at least twelve samples per testing variable;
  - c. provide the complete dissolution profile data (*individual, mean, SD, profiles*) for your product. The dissolution data should be reported as the cumulative percentage of drug dissolved with time (*the percentage is based on the product's label claim*); and
  - d. include the testing conducted to demonstrate the discriminating capability of the selected dissolution test as well as the supportive validation data for the dissolution method (*i.e., method robustness, etc.*) and analytical method (*precision, accuracy, linearity, stability, etc.*).
2. **Dissolution Acceptance Criterion:** For the selection of the dissolution acceptance criterion of your product, the following points should be considered:
- a. The dissolution profile data from the clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your product (*i.e., specification-sampling time point and specification value*).
  - b. The *in vitro* dissolution profile should encompass the timeframe over which at least  $\frac{(b)}{(4)}$ % of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.
  - c. For immediate release product the selection of the specification time point should be where  $Q = \frac{(b)}{(4)}$ % dissolution occurs.

Note that the final determination on the acceptability of the proposed acceptance criteria for your product will be made during NDA review process based on the totality of the provided data.

### Discussion

The Sponsor explained that since ponatinib is a nonsterile oral drug product produced by  $(b) (4)$   $(b) (4)$  particle size testing would not be performed. The Sponsor is also proposing to justify 'reduced microbial limits testing' by creating a data set for the Agency's review, comprised of testing under GMP, per USP <1112>, water activity, and continue testing per USP <1111> and by USP <61>, in order to reduce microbial enumeration testing, if justified.

The Agency explained that, if an attribute is included in the drug product specification, testing should be performed for every batch. The Agency also explained that, in order to justify the removal of microbial limits testing, drug product batch data for this attribute should be collected throughout development and submitted in the NDA. The acceptability of this information will be determined at the time of NDA review.

*The Sponsor agreed to provide all information including the justification for the removal of microbial limits testing in the drug product specifications in the NDA.*

### **Additional Comments**

The Agency appreciates your approach to apply QbD based principles for drug substance and drug product development. Note, that in general, the Agency does not encourage the use of the term '(b) (4)' associated with design space, since '(b) (4)' typically means univariate ranges, that are determined by One Factor At a Time (OFAT) experiments. However, we do recognize that the term '(b) (4)' has different meanings in different companies, thus would like clarification of your definition of '(b) (4)' included in your submission. The design space should contain the parameters that have potential to affect product quality and include a consideration of interactions, when appropriate. Furthermore, to support your QbD implementation approach, consider providing the following information in your NDA submission:

- The scientific rationale for designation of the Quality Target Product Profile (QTPP) and identification of corresponding drug substance / drug product Critical Quality Attributes (CQAs) that have an impact on the QTPP.
- Risk based justification for selection of parameters to define the design space. Furthermore, it is recommended while assessing risks of process parameters/material attributes that you consider impact of interaction of parameters as well as effects of equipment and/or scale.
- When DOE's are used to define design space, a graphical or tabular summary of input data that shows the multivariate combinations used and the statistical analysis relating the process inputs to the responses.
- A description of the approach, along with appropriate supporting data, for scale up of the design space from lab to commercial scale (if applicable) and verification of the design space at commercial scale.
- A discussion of the potential effect of excipient variability on product quality when manufacturing within the design space.
- A description of your control strategy that ensures the manufacture of acceptable quality product within the design space.

### **Discussion**

*The Sponsor clarified their use of the term '(b) (4)' and included the intent to avoid the use of the term '(b) (4)' in their NDA submission. The Agency stated that the Sponsor's proposal appears reasonable and emphasized that the additional information provided in the preliminary responses was intended as an FYI regarding recommendations related to the proposed QbD approach.*

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

No issues requiring further discussion were identified during this meeting.

#### **4.0 ACTION ITEMS**

The Agency identified no action items for this meeting. The Sponsor expressed their intention to submit the requested dissolution data within a month of the meeting.

#### **Post Meeting Comments**

In response to Question 2, the Sponsor sent an e-mail dated February 11, 2011, confirming that the (b) (4) specification was submitted in an IND amendment on April 23, 2009.

Agency Response: During the teleconference, the Sponsor clarified that batch analysis data for AP24534 showed very low levels and in some batches non-detectable levels of (b) (4). As a follow up meeting comment, the Agency recommends that the Sponsor revise the proposed acceptance criteria based on data obtained from analysis of batches of drug substance and safety considerations. Submit this as an amendment to the IND that includes a summary of (b) (4) (b) (4) levels in the drug product that were administered to patients on a mg/kg basis in the phase 1 trials. Also provide the number of patients exposed to different levels of (b) (4). Note that the acceptability of this information to support the forthcoming NDA will be determined during the NDA review.

#### **5.0 ATTACHMENTS AND HANDOUTS**

Presentation - Clarification of FDA Questions & Responses

E-mail – Follow-up Telephone call to the FDA Teleconference 10 February 2011

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